Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

AMG 103/Blinatumomab

MK-3475/Pembrolizumab

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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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Investigator's Agreement

I have read the attached protocol entitled A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in combination **W**ith Pembrolizumab in Adult Subjects **W**ith Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL), dated **03 December** 2019, and agree to abide by all provisions set forth therein.

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I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

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Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Study Phase: 1b

Indication: Adult Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Primary Objective:

- To determine the maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab in adult subjects with relapsed or refractory (r/r) DLBCL

Secondary Objective(s):

- To evaluate the safety, efficacy, and pharmacokinetics (PK) of blinatumomab in combination with pembrolizumab in adult subjects with r/r DLBCL

Hypotheses:

The overlying hypothesis is that blinatumomab in combination with pembrolizumab will be tolerable in r/r DLBCL.

Primary Endpoints:

- Incidence of dose limiting toxicities (DLTs)

Secondary Endpoint(s):

- Objective response (OR) **(including CR and PR)** by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab and during the treatment period**
- Complete re**sponse** (CR) by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab and during the treatment period**
- Duration of response (DOR) **for subjects with** OR **(ie,** CR and partial remission **[**PR**])** **by the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab**
- Progression free survival
- Overall survival (OS)
- Blinatumomab PK parameters
- Pembrolizumab PK parameters

Safety Endpoints:

- Incidence and severity of adverse events

Study Design:

This is an open label, multicenter, phase 1b study testing the combination of blinatumomab with pembrolizumab in r/r DLBCL.

The study will consist of 2 portions:

- Part 1 (n = 6 – 30) will test the safety of up to 3 different blinatumomab target dose levels in combination with pembrolizumab in a rolling 6 design. A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and DLTs. Subjects who are not on the dose ultimately selected for part 2 will remain on their initial dose throughout the study.
- Part 2 (n = **40**) will consist of an expansion cohort to assess PK, safety, and preliminary efficacy data at the chosen target dose. The part 2 dose will be determined by the totality of the clinical data from part 1 as determined by the DLRT.

The study design includes:

- A 21-day screening period
- A standard (core) treatment period of blinatumomab (first cycle) of 8 weeks
- A second (consolidation) cycle of blinatumomab of 28 days after a 28-day (± 3 days) blinatumomab treatment free period, that can be administered to subjects with stable disease (SD), PR, or CR.
- Pembrolizumab treatment until disease progression or up to 35 cycles in the absence of disease progression:

  –To begin on study day 15 for subjects in cohort Ia

  OR

  –To begin on study day 19 for subjects in cohort IIa and IIIa
- A safety follow-up visit after 30 days (+ 7 days) of last dose of each protocol specified therapy.

Follow-up for survival and collection of subsequent anticancer therapies will occur every 12 weeks (± 28 days) for following blinatumomab safety follow-up visit until approximately 24 months from the last dose of pembrolizumab.

For complete details regarding design and escalation rules, please refer to Section 3.

Sample Size: A maximum of approximately **70** subjects will be enrolled.

Summary of Subject Eligibility Criteria: This study seeks to enroll adult subjects with histologically confirmed DLBCL that is either refractory after at least one regimen of systemic chemotherapy and/or targeted therapy, or in first or later relapse if have received at least 2 systemic regimens since time of diagnosis, or relapsed post-autologous or allogeneic hematopoietic stem cell transplantation with adequate organ function after proximity to transplantation time exclusions as specified in Exclusion Criteria 208 and 209.

Subjects will be excluded if they have Richter's transformation (DLBCL arising in the setting of prior chronic lymphocytic leukemia) or Primary Mediastinal B-cell Lymphoma (PMBCL) or have history or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis or has evidence of active, non-infectious pneumonitis, or has a history of interstitial lung disease.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Blinatumomab is administered as a continuous intravenous infusion (CIVI). The first cycle of blinatumomab treatment is 8 weeks **(56 days) of standard blinatumomab continuous infusion** followed by a 28-day (± 3 days) blinatumomab treatment-free interval. The initial dose of blinatumomab will be 9 µg/day and will be dose escalated at weekly intervals until the target dose is reached. If a subject meets the requirements for continuing study therapy, they may receive another cycle of blinatumomab (cycle 2 consolidation cycle) **consisting** of 28 days **standard blinatumomab continuous infusion** after a 28-day (± 3 days) treatment free interval. The consolidation cycle dosing will be the same as the first 28 days of cycle 1 of blinatumomab, starting at 9 µg/day with weekly dose escalations until the target dose is reached.

Non-Amgen Investigational Product Dosage and Administration: Pembrolizumab 200 mg will be administered intravenously (IV) for 30 minutes every 3 weeks [Q3W] starting on study day 15 in cohort Ia, and on study day 19 in cohorts IIa and IIIa (3-week cycle). Pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

Procedures: Written informed consent must be obtained from all subjects or legally acceptable representatives before any study specific procedures are performed. The following procedures will occur per the Schedule of Assessments: medical history, demographics, Eastern Cooperative Oncology Group (ECOG) performance status, neurological examination, physical exam including height, weight, vital signs, concomitant medications, adverse event/serious adverse event assessment, **and** disease related events. The subjects will undergo radiologic assessments (brain magnetic resonance imaging [MRI], computed tomography [CT] scan, and positron emission tomography [PET] scan) per the time points outlined in the Schedule of Assessments. Samples will be collected for local laboratory testing including: bone marrow biopsy, lumbar puncture, chemistry, coagulation, hematology (complete blood count [CBC]), immunoglobulins, urinalysis, thyroid function tests, creatinine clearance [CrCl], and pregnancy test. The subjects will further provide samples for central laboratory testing including: anti-blinatumomab antibodies, anti-pembrolizumab antibodies, immune panel, serum cytokines, PK (blinatumomab and pembrolizumab), core or incisional/excisional biopsy for biomarker analysis **(optional)**, and minimal residual disease (MRD) by next generation sequencing (NGS) as indicated in the Schedule of Assessments.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4).

Statistical Considerations:

General consideration:

Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including estimates of Kaplan-Meier (KM) quartiles, KM proportions, and binomial proportions. Pharmacokinetics will be performed by noncompartmental analysis. Pharmacodynamic samples will be summarized by descriptive statistics.

Sample Size Considerations

Part 1: A rolling 6 dose design will be used. An additional 4 subjects can be enrolled per cohort to further evaluate safety and PK data if needed. There will be a minimum of 6 subjects and a maximum of 30 subjects enrolled.

Part 2: **Forty subjects will be enrolled to estimate objective response rate (ORR).**

Interim Analyses

Efficacy and safety will be assessed.

For efficacy, the Bayesian approach will be used to calculate the posterior probability of objective response rate (ORR) using the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab < 50% for every 10 subjects enrolled. If the posterior probability is > 80%, the trial may be stopped.

For safety, the Bayesian approach will be used to calculate the upper boundary of a DLT rate of 25% for **every 10** subject**s** enrolled. If the number of DLT-qualifying adverse events observed crosses the boundary, the trial will be stopped.

Primary Analysis

The primary analysis will occur after the last subject in part 2 has had an opportunity to **complete response** assessment **during** 12 weeks **since** starting blinatumomab.

Final Analysis

The final analysis of OS will occur when the last subject assigned to treatment with blinatumomab has had the opportunity to complete the long-term follow-up period, which is following blinatumomab safety follow-up visit until approximately 24 months after the last dose of pembrolizumab. For a full description of statistical analysis methods, please refer to Section 10.

Study Design and Treatment Schema

Figure 1. Study Design and Treatment Schema

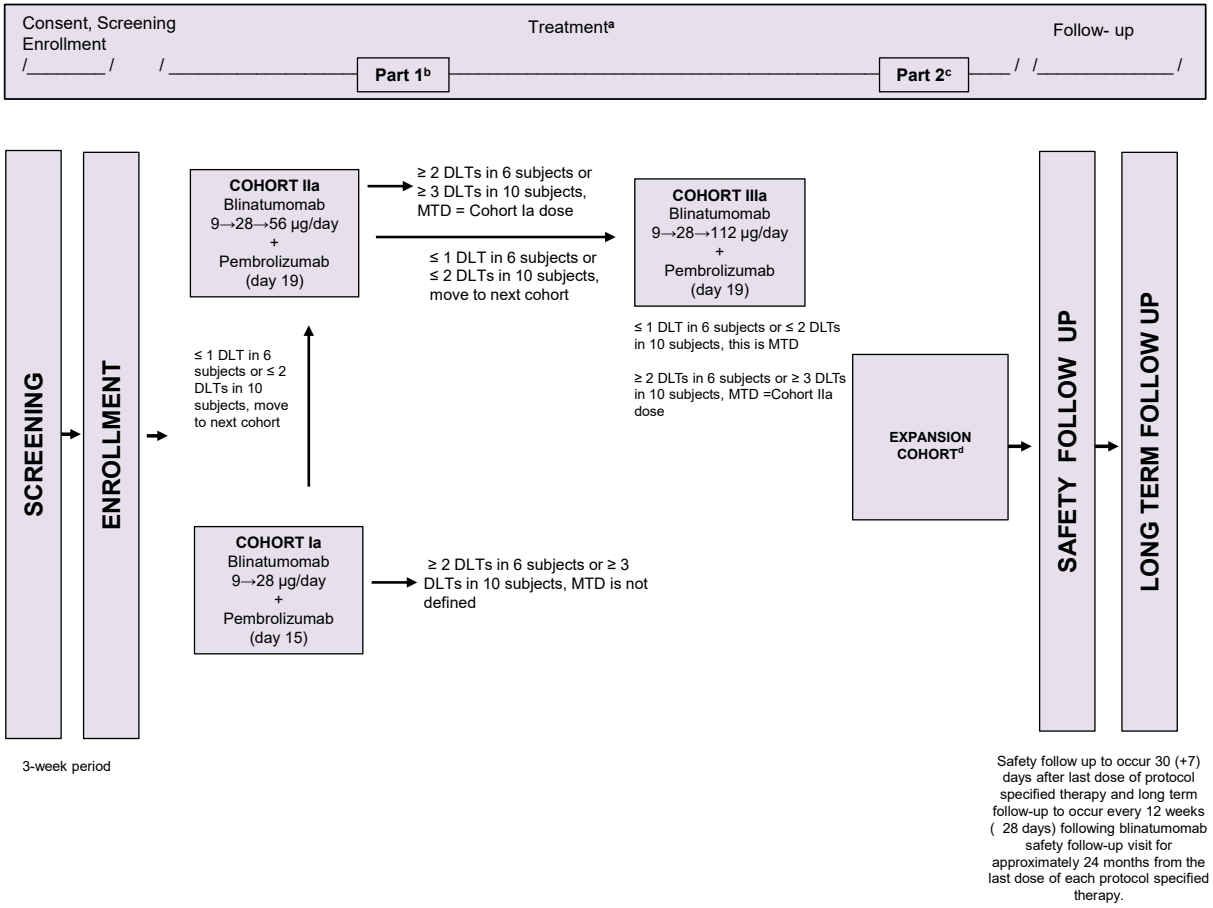

Figure legend defined on the next page

CRS = cytokine release syndrome; DLT = dose limiting toxicity; MTD = maximum tolerated dose
First cycle of blinatumomab will be 8 weeks in duration, followed by a 28-day (± 3 days) blinatumomab treatment-free interval. A second consolidation cycle of blinatumomab will be 28 days in duration at the same dose as the first cycle, starting at 9 µg/day with weekly dose escalations until the target dose is reached, if subject has stable disease or partial/complete remission after cycle 1. Pembrolizumab will be started on study day 15 for cohort Ia, and study day 19 for cohorts IIa and IIIa, and administered Q3 weeks until disease progression for up to 35 cycles. **The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1). The first dose of pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events, no > grade 1 CRS and/or neurologic events.** The cohort names have been updated to be in sequential order, retaining the historical "a" in the cohort name (ie, cohorts Ia, IIa, IIIa) from previous protocol naming convention.
[a] For cohorts Ia, IIa and IIIa, the DLT observation period will begin on the same day as the first dose of pembrolizumab (day 15 for Ia and day 19 for IIa and IIIa) and will continue for 42 days. For part 2, the DLT observation period will be determined by the cohort chosen in part 1 for the part 2 expansion. A dose level review team (DLRT) will review the available data to determine if blinatumomab is safe and tolerable as defined by DLT criteria and general clinical judgement. Based on the totality of the data, the DLRT may recommend to declare MTD, to escalate to the next dose level, to expand a cohort to a maximum of 10 subjects if the collection of more data is deemed warranted, or to adjudicate the DLT criteria (see Appendix E for details).
[b] Part 1: To determine MTD of blinatumomab in combination with pembrolizumab. The MTD will be defined as the dose level at which ≤ 1 DLT in 6 subjects or ≤ 2 DLTs in 10 subjects experience a DLT.
[c] Part 2: Expansion cohort to estimate the efficacy of the combination of blinatumomab and pembrolizumab. Dosing will be determined based on the MTD of blinatumomab established in part 1. Dose limiting toxicities **and efficacy** will be monitored **by the Data Review Team** to ensure they do not reach a pre-defined threshold **of 25%**.
[d] Dosing for the part 2 expansion cohort will be based on the safety of the combination of blinatumomab and pembrolizumab and the MTD of blinatumomab in part 1.

Study Glossary

Abbreviation or Term	Definition/Explanation
aaIPI	age adjusted International Prognostic Index
ABC	activated B-cell
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANA	anti-nuclear antibody
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BCL	B-cell lymphoma
BiTE	bispecific T-cell engager
CAR-T	chimeric antigen receptor t-cell
CBC	complete blood count
CD	cluster of differentiation
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CIVI	continuous intravenous infusion
CNS	central nervous system
COO	cell-of-origin
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CR	complete remission
CrCl	creatinine clearance
CRF	case report form
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic t lymphocyte
CTLA-4	cytotoxic t-lymphocyte antigen-4
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DLBCL	diffuse large B-cell lymphoma
DLRT	Dose Level Review Team
DLT	dose limiting toxicity

Abbreviation or Term	Definition/Explanation
DOR	duration of response
DRT	**Data Review Team**
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDC	electronic data capture
EMA	European Medicines Agency
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Each Subject	defined as the date the subject withdraws full consent from the study, completes the safety follow-up visit, or final long-term follow-up visit (whichever is later), or death
End of Study (end of trial)	defined as when the last subject across all sites is assessed or receives an intervention for evaluation of the study (ie, last subject last visit), following any additional parts in the study (eg, long term follow-up)
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
eSAE	electronic serious adverse event
EU	European Union
FBR	future biomedical research
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
GC	germinal center
GCP	good clinical practice
GI	gastrointestinal
GvHD	graft versus host disease
HBc	hepatitis b core
HBs	hepatitis b surface
HBV	hepatitis b virus
HCV	hepatitis c virus
HLGT	High-level Group Term
HIV	Human Immunodeficiency Virus
HSCT	hematopoietic stem cell transplantation
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors

Abbreviation or Term	Definition/Explanation
IFN-γ	interferon-gamma
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV-type	immunoglobulin variable-type
IL	interleukin
INR	international normalized ratio
IPI	international prognostic index
IPIM	investigational product instruction manual
irAE	Immune-related adverse event
IRB/IEC	institutional review board/independent ethics committee
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
JAK	Janus Kinase
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LKM1	Liver Kidney Microsomal antibody 1
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NASH	Nonalcoholic Fatty Liver Disease including Steatohepatitis
NCI	National Cancer Institute
NFkB	nuclear factor kappa B
NGS	next generation sequencing
NHL	Non-Hodgkin Lymphoma
NK	natural killer
NSCLC	non small-cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD-1	programmed cell death-1
PET	positron emission tomography

Abbreviation or Term	Definition/Explanation
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PFS	progression free survival
PK	pharmacokinetics
PKCθ	protein kinase C-theta
PMBCL	Primary Mediastinal B-cell Lymphoma
POR	proof of receipts
PR	partial remission
PTEN	phosphatase and tensin homolog
Q2W	every 2 weeks
Q3W	every 3 weeks
R-ACVBP	rituximab, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone
R-CHOP	rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP	rituximab, dexamethasone, cytarabine, cisplatin
RICE	rituximab, ifosfamide, carboplatin, etoposide
r/r	relapsed or refractory
ROW	rest of the world
SD	stable disease
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	type 1 diabetes mellitus
TBL	total bilirubin
TEAE	**treatment-emergent adverse event(s)**
TNF-α	tumor necrosis factor-alpha
TMDD	target-mediated drug disposition
T-regs	regulatory T-cells
ULN	upper limit of normal
WES	whole exome sequencing
WHO	World Health Organization
WHODRUG	World Health Organization Drug
ZAP	zeta-chain-associated protein kinase

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1. OBJECTIVES

1.1 Primary

- To determine the maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab in adult subjects with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL).

1.2 Secondary

- To evaluate the safety, efficacy, and pharmacokinetics (PK) of blinatumomab in combination with pembrolizumab in adult subjects with r/r DLBCL.

1.3 Exploratory

- To evaluate blood and tissue biomarkers.
- To evaluate minimal residual disease (MRD) response by next generation sequencing (NGS).

2. BACKGROUND AND RATIONALE

2.1 Disease

The annual incidence of Non-Hodgkin Lymphoma (NHL) in Europe and the USA is estimated to be 15 to 20 cases/100,000 (Fisher and Fisher, 2004). Diffuse Large B-Cell Lymphoma is the most common lymphoid malignancy in adults, accounting for 31% of all NHL in Western countries and 37% of all B-cell tumors worldwide (NHL classification project, Blood 1997; Swerdlow et al, WHO classification 2016). The peak incidence of DLBCL is in the seventh decade (Martelli et al, 2013), with incidences increasing from 0.3/100.000/y (35-39 years) to 26.6/100,000/y (80-84 years; Morgan et al, 1997).

According to the World Health Organization (WHO) classification, DLBCL corresponds to a group of lymphoid malignancies composed of large cells with vesicular nuclei, prominent nucleoli, basophilic cytoplasm and an unusually high proliferation rate. Diffuse large B-cell lymphoma is biologically and clinically heterogeneous, with subgroups defined by morphology, immunophenotype, genetic alterations, and transcriptional patterns. Although most cases arise de novo, some are progression or transformation of less aggressive lymphoma, eg, chronic lymphocytic leukemia or follicular lymphoma (Hartge and Wang, 2004). Despite this heterogeneity, and with the exception of cases in which disease involves the central nervous system (CNS) DLBCL, DLBCL is generally treated in a consistent manner (Gisselbrecht et al, 2010).

Immunophenotyping is an essential diagnostic procedure which allows DLBCL to be identified and allows DLBCL to be further divided into germinal center (GC) type (cluster of differentiation [CD]10+ or CD10-, B-cell lymphoma 6 protein [BCL6] + mouse

monoclonal [MUM1-]) and non GC type (CD10-, BCL6- or CD10-, BCL6+, MUM1+; Hans et al, 2004). Germinal center/non-GC stratification by the Hans algorithm provides valuable prognostic information, but the supporting data is derived primarily from patients treated in the pre-rituximab era. Its prognostic value is less clear in patients treated with immunochemotherapy as opposed to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) alone (Nyman et al, 2007). Alternatively, prognostic differentiation can be achieved with gene expression profiling (Rosenwald et al, 2002) subdividing DLBCLs into GC types, activated B-cell (ABC) types and also Primary Mediastinal B-cell Lymphoma (PMBCL). The prognostic stratification between GC and ABC sub-types remains valid in patients receiving immunochemotherapy (Lenz et al, 2008).

The GC-like lymphomas probably arise from normal GC B-cells and are associated with the t(14;18) translocation, deletion of phosphatase and tensin homolog (PTEN), amplification of the micro RNA cluster-17-92 (miR-17-92), and protein 53 (p53) mutations. The ABC Lymphomas are thought to originate from a post-GC B-cell and are characterized by activation of the nuclear factor kappa B (NFkB) and Janus Kinase (JAK) signalling pathways (Lenz and Staudt, 2010).

The International Prognostic Index (IPI) and age-adjusted IPI (aaIPI) have been developed as models for predicting outcomes based on clinical factors (The international NHL prognostic factors project, 1993).

Table 2-1. Age-adjusted International Prognostic Index (aaIPI) for DLBCL

aaIPI	
Risk group	IPI Factors
Low	0
Low Intermediate	1
High Intermediate	2
High	3

aaIPI Factors:
Disease stage III/IV
Lactate dehydrogenase level elevated
ECOG performance score ≥ 2
DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index

The aaIPI is widely used for stratification and analysis of clinical trials. A revised version has been developed in the postrituximab era and is currently still under evaluation (Sehn et al, 2007).

Treatments

Overall, DLBCLs are aggressive but potentially curable malignancies. Cure rate is particularly high in patients with limited disease with a 5-year progression free survival (PFS) ranging from 80 to 85%. Patients with advanced disease or symptomatic disease have a 5-year PFS of approximately 50%.

The choice of the first line treatment for patients with DLBCL is based on the individual IPI score and age. This leads to 3 major subgroups of DLBCL patients: elderly patients (> 60 years, aaIPI = 0-3), young patients with low risk (≤ 60 years, aaIPI = 0-1) and young patients with high risk (≤ 60 years, aaIPI = 2-3; Martelli et al, 2013). Rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) given every 14 or 21 days is the cornerstone of first-line therapy for DLBCL (Zelenetz et al, 2016; Tilly et al, 2015), particularly for elderly patients and younger patients with low risk features. For elderly patients, the introduction of a so called pre-phase treatment consisting of vincristine and prednisone may help reduce toxicities. Younger patients with low risk features may also be treated with rituximab, doxorubicin, cyclophosphamide, vincristine, bleomycin, and prednisone (R-ACVBP) without radiotherapy or R-CHOP21 with radiotherapy for bulky disease. Young patients with high risk represent the greatest current challenge in the front-line treatment of DLBCL. Around 30% of these patients are refractory to front-line R-CHOP. Several options in addition to R-CHOP are being considered, including enrollment in clinical trials or use of high dose chemotherapy with autologous hematopoietic stem cell transplantation (HSCT). Autologous HSCT is currently only recommended in eligible patients with DLBCL who did not achieve complete response after first line chemotherapy or in patients with chemosensitive relapse (Barosi et al, 2005).

Despite the improvements observed since the introduction of rituximab into front-line treatments, relapse is observed in 10-20% of patients with low IPI and 30-50% in high IPI patients. **Additionally, there are about 10-20% refractory patients who do not respond to or progress on treatments (Gisselbrecht and Van Den Neste, 2018; Coiffier and Sarkozy, 2016). In more recent studies and the regulatory approval, the refractory disease is defined as progressive or stable disease as the best response to the most recent systemic chemotherapy regimen or disease progression or relapse within 12 months after autologous stem cell transplantation (Crump et al, 2017; Neelapu et al, 2017); when using the positron emission tomography (PET) scan for response assessment after radiation therapy**

or chemotherapy plus radiation, to minimize the confounding factor of post-therapy inflammatory changes, the PET scans should not be performed for at least 3 weeks, and preferably 6 to 8 weeks, after completion of therapy (Cheson et al, 2007). Various salvage regimens are currently used in r/r DLBCL. The CORAL study demonstrated no differences in response rates when using either rituximab, ifosfamide, carboplatin, etoposide (RICE) or rituximab, dexamethasone, cytarabine (also known as Ara-C) and cisplatin (R-DHAP) followed by autologous HSCT, with an objective response rate (ORR) of 63%. One-third of patients did not respond to chemotherapy and only one half were able to proceed to autologous HSCT. Outcomes were particularly poor for patients that had received prior rituximab or had relapsed within 1 year of diagnosis (Gisselbrecht et al, 2010). Allogeneic HSCT is considered for a select group of patients with relapsed DLBCL (Friedberg, 2011). However, this treatment is associated with a high treatment-related mortality rate (up to ~25%).

For patients who have an inadequate response to, or who are not candidates for intensive salvage regimens or HSCT, prognosis is poor with no defined standard of care.

Due to the high medical need in these patients new molecules are being investigated (see Table 2-2).

Table 2-2. Investigational Agents in Patients Who Have an Inadequate Response to, or Who are Not Candidates for Intensive Salvage Regimens or HSCT

Regimen	ORR	CR/Cru	RD/RFS/EFS/PFS rate	OS rate	Reference
Lenalidomide	28%	7%	NK	NK	Witzig et al, 2011
R-Bendamustin	53%	12%	NK	NK	Vacirca et al, 2010
Temsirolimus	28%	12%	NK	NK	Smith et al, 2010
Yttrium epratuzumab	19%	12%	NK	NK	Morschhauser et al, 2010
Bortezomib	8%	NK	TTP 1.8 mo	NK	Goy et al, 2005
Ofatumomab	11%	4%	PFS 2.5 mo	NK	Salles et al, 2012
GA 101	28%	4%	PFS 83 d	NK	Gabellier and Cartron, 2016
Bevacizumab	2%	NK	RD 5.2 mo	NK	Stopeck et al, 2009
Inotuzumab ozogamicin	15%	8%	PFS 49 d	NK	Advani et al, 2010
Yttrium 90 ibritumomab	19%	12%	PFS 1.6 mo	NK	Fiona and Ruth, 2007
Pixantrone	41%	23%	PFS 5.7 mo	NK	Pettengell et al, 2012
SAR3419	44%	NA	NK	NK	Trneny et al, 2014
R-Inotuzumab	74%	NA	PFS rate at 2 years 42%	NK	Dang et al, 2014

CR = complete response; Cru = complete response unconfirmed; EFS = event free survival; HSCT = hematopoietic stem cell transplantation; NA = not applicable; NK = not known; ORR = objective response rate; OS = overall survival; PFS = progression free survival; RD = response duration; RFS = relapse free survival; TTP = time to progression

As can be seen from Table 2-2, most molecules had unsatisfactory response rates, particularly the CR rates, which are important for the long-term outcomes of patients. Remissions are usually not of long duration and often come at the price of severe toxicities. Based on the data presented in Table 2-2, the only molecule which has received market approval recently was pixantrone, which was conditionally approved in Europe. Thus, additional therapeutic approaches are urgently needed.

Blinatumomab is a bispecific T-cell engager (BiTE®) designed to direct cytotoxic T cells to CD19-expressing cancer cells. CD19 is highly expressed throughout B cell development and is present on > 90% of B-cell lineage cancers including DLBCL (Zimmerman et al, 2015). In a phase 1 study of patients with relapsed or refractory DLBCL who received blinatumomab at 60 µg/m^2 (n = 11), the CR rate was 36%, the ORR was 55% and median duration of response (DOR) was 404 days (95% CI,

207-1129 days) (Goebeler et al, 2011). A subsequent open-label phase 2 study (MT103-208) in adults with r/r DLBCL demonstrated stepwise dosing with weekly dose escalation of blinatumomab (9 to 28 to 112 µg/day) was tolerable and associated with antitumor activity with an ORR of 42.9% for evaluable patients and a CR rate of 16% (Viardot et al, 2014). Duration of response ranged from 26 to 533 days. The most common adverse events were tremor, pyrexia and fatigue. Grade 3 and higher neurologic adverse events were reported in 6/23 (26.1%) of subjects treated in the step-dosing cohort, but were generally reversible with treatment interruption.

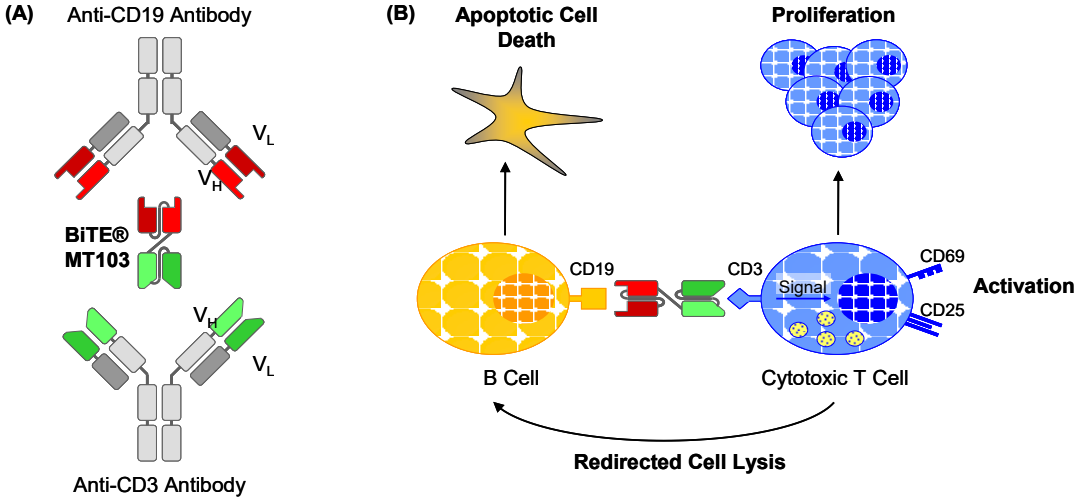
2.2 Amgen Investigational Product Background: Blinatumomab

Blinatumomab (BLINCYTO®, AMG 103, formerly also known as MT103 or bscCD19xCD3) is a member of a novel class of bispecific antibody constructs called BiTE®, or bispecific T-cell engagers (Dreier et al, 2002; Schlereth et al, 2006). Blinatumomab is a BiTE® antibody construct with dual binding specificities. T cells are bound by the anti-CD3 moiety, whereas B lymphoblasts and other B cells are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T cell mediated killing of the bound malignant cell.

Blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor acute lymphoblastic leukemia (ALL) cells, with an affinity of 1.6×10^{-9} M. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (8.7×10^{-8} M). These activated T cells then induce a half-maximal target cell lysis ranging in vitro between 10 to 100 pg/mL showing blinatumomab to be an extremely potent molecule (Dreier et al, 2002).

During the course of tumor cell elimination, activated T cells synthesize and secrete pro-inflammatory cytokines as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-6, and IL-2, which might induce symptoms such as fever or decreases of blood pressure. In vitro data demonstrate cytokine release as a result of blinatumomab-mediated T-cell activation, which can be attenuated by corticosteroids without impairing the cytotoxic activity. In vivo data indicate cytokine release to be most prominent following the first dose of blinatumomab.

Figure 2. Mode of Action of Blinatumomab



Due to its unique ability to redirect T cells via CD3 towards a $CD19^+$ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed $CD4^+$ and $C8^+$ T cells. The antitumor activity is effective within a wide range of effector to target (E:T) ratios.

In the absence of $CD19^+$ target cells neither cytotoxicity nor release of cytokines will occur. Blinatumomab acts strictly in a target cell specific and dependent manner, with regard to cytotoxic action. The presence of both $CD19^+$ target cells and T cells are required for its cytotoxic activity.

As of July 2017, blinatumomab (BLINCYTO) is indicated for the treatment of relapsed or refractory B-cell precursor ALL in the United States. It is indicated in multiple countries outside of the United States for Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (eg, European Union [EU], Mexico, Canada, Norway, Iceland, Australia, and South Korea).

Additionally, confirmation of clinical benefit is a condition of approval in multiple countries (eg, European Medicines Agency [EMA]).

Refer to the Blinatumomab Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Non-Amgen Medicinal Product Background: Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death-1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2). Based on preclinical in vitro data,

pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advance malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the Pembrolizumab Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

Therapeutic studies of pembrolizumab in mouse models have shown that administration of antibodies blocking PD-1/PD-L1) interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Spranger et al, 2014; Curran et al, 2010; Pilon-Thomas et al, 2010; Weber, 2010; Hirano et al, 2005; Blank et al, 2004; Strome et al, 2003). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Curran et al, 2010; Pilon-Thomas et al, 2010; Zhang et al, 2009; Nomi et al, 2007; Strome et al, 2003). In such studies, tumor infiltration by CD8+ T-cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran et al, 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Pembrolizumab Investigator's Brochure).

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis et al, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al, 2005; Hunder et al, 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. Programmed cell death-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated lymphocyte 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al, 2005; Okazaki et al, 2001). The structure of murine PD-1 has been resolved (Zhang et al, 2004).

Programmed cell death-1 and its family members are type I transmembrane glycoproteins containing an immunoglobulin (Ig) variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ) and zeta-chain-associated protein kinase (ZAP)70, which are involved in the CD3 T cell signaling cascade (Chemnitz et al, 2004; Okazaki, et al, 2001; Riley, 2009; Sheppard et al, 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 because both molecules regulate an overlapping set of signaling proteins (Parry et al, 2005; Francisco, 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.

2.4 Rationale

Rationale for combining Pembrolizumab and Blinatumomab:

Both PD-L1 and soluble PD-L1 expression has been reported in DLBCL and the expression of these ligands has been correlated with an inferior prognosis (Andorsky et al, 2011). Immune checkpoint inhibitors including pembrolizumab are being actively investigated in hematologic malignancies and have demonstrated single agent activity in lymphomas including DLBCL (Kiyasu et al, 2015; Lesokhin et al, 2016). The KEYNOTE-013 trial is currently testing pembrolizumab in a cohort of DLBCL subjects.

Furthermore, pre-clinical studies of blinatumomab have identified involvement of the PD-1/PD-L1 axis as a potential mechanism of resistance to BiTE® mediated therapy. In r/r ALL, upregulation of PD-L1 has been observed on lymphoblasts of a patient receiving blinatumomab (Köhnke et al, 2015) and in vitro blockade of the PD-1/PD-L1 axis augmented lysis of acute myelogenous leukemia (AML) cells by the CD33/CD3 BiTE® antibody construct AMG-330 (Krupka et al, 2016). In line with these data, using AML cell lines engineered to ectopically overexpress individual T cell ligands, Lazlo et all demonstrated that the expression of PD-L1 and PL-L2 significantly reduced the anti-leukemic activity of AMG-330 (Lazlo et al, 2015). Similarly, Kenderian et al (Kenderian et al, 2016) showed that incubation of primary AML samples with either CD-123 chimeric antigen receptor t-cell (CAR-T) or CD-33 CAR-T resulted in a significant upregulation of PD-1 on AML T cells and PD-L1 on AML blasts. Using an AML xenograft model, they demonstrated that combination of a blocking PD-1 antibody plus CD-33 or CD-123 CAR-T enhanced the anti-leukemic activity of the single agent by significantly prolonging survival. In vitro dual blockade of PD-1 and PD-L1 with a CEA-BiTE enhanced cytolytic activity of the BiTE on solid tumors (Osada et al, 2015). Finally, pediatric patients with ALL demonstrated increased expression of PD-L1 on leukemic blasts and combined treatment with blinatumomab and pembrolizumab was feasible and induced a response in a pediatric patient with ALL relapsed allogenic HSCT (Feuchtinger et al, 2015). Together, these data suggest that pembrolizumab could both unleash a polyclonal immune response against endogenous tumor antigen as well as enhance the CD-19 specific immune response elicited by blinatumomab, potentially leading to a synergistic effect.

Rationale for Pembrolizumab Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non small-cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

Rationale for Blinatumomab Dose:

Three target doses will potentially be tested in part 1 in a dose-escalation design starting at the lowest blinatumomab target dose of 28 µg/day with the primary focus on identifying a safe combination dose. Blinatumomab will be escalated in a stepwise

manner until the appropriate target dose is reached. This dosing paradigm is based on safety and efficacy data from the phase 1 Study MT103-104 in NHL (including DLBCL) and the phase 2 Study MT103-208 in DLBCL in which blinatumomab was tested as a monotherapy.

Step dosing of blinatumomab has been implemented to mitigate the potential for adverse events associated with excessive T cell activation and cytokine release. Blinatumomab has been associated with transient elevation of serum cytokines, especially IL-6, IL-10, and IFN-γ, the cytokine elevation largely occurred within the first two days following the initial dose of blinatumomab (Armand et al, 2013).

Accordingly, adverse events potentially related to T-cell activation and cytokine release, such as cytokine release syndrome (CRS) and neurologic events are more frequent at the time of initiation of blinatumomab treatment. Step-wise dosing has been shown to attenuate the cytokine release and reduce the occurrence/severity of those events in previous studies (MT103-104 and MT103-208).

In the MT103-208 study, grade 3 or higher neurologic treatment emergent adverse events were reported in 21.7% of subjects receiving stepwise dosing and 100% of subjects receiving flat dosing with a median time to onset of 18 days. No CRS was reported in MT103-208, however grade 3 CRS was reported in 2% of subjects on Study MT103-211 in r/r ALL with a median time to onset of 2 days.

Part 2 will consist of an expansion cohort to ensure adequate safety and PK data is collected. The blinatumomab target dose will be based on safety data from part 1.

Since the majority of blinatumomab associated adverse events occur near time of initiation or dose step, in each blinatumomab dose level cohort, the addition of pembrolizumab will first be tested after the blinatumomab target dose has been reached. See Figure 1 for the treatment schema.

To minimize the risk of CRS and neurologic events, all patients will receive prophylactic dexamethasone (see Table 6-4).

2.5 Clinical Hypotheses

The overlying hypothesis is that blinatumomab in combination with pembrolizumab will be tolerable in r/r DLBCL.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open label, multicenter, phase 1b study testing the combination of blinatumomab with pembrolizumab in r/r DLBCL.

The study will consist of 2 portions:

- Part 1 (n = 6 – 30) will test the safety of up to 3 different blinatumomab target dose levels in combination with pembrolizumab in a rolling 6 design. A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and dose limiting toxicities (DLTs). Subjects who are not on the dose ultimately selected for part 2 will remain on their initial dose throughout the study.
- Part 2 (n = **40**) will consist of an expansion cohort to assess PK, safety, and preliminary efficacy data at the chosen target dose. The part 2 dose will be determined by the totality of the clinical data from part 1 as determined by the DLRT.

The study design includes:

- A 21-day screening period.
- A standard (core) treatment period of blinatumomab (first cycle) of 8 weeks
- A second (consolidation) cycle of blinatumomab of 28 days after a 28-day (± 3 days) blinatumomab treatment-free period that can be administered to subjects with stable disease (SD), partial remission (PR), or CR.
- Pembrolizumab treatment until disease progression or up to 35 cycles in the absence of disease progression:
  - To begin on study day 15 for subjects in cohort Ia

    OR
  - To begin on study day 19 for subjects in cohort IIa and IIIa
- A safety follow-up visit after 30 days (+ 7 days) of last dose of each protocol specified therapy.

Follow-up for survival and collection of subsequent anticancer therapies will occur every 12 weeks (± 28 days) following blinatumomab safety follow-up visit until approximately 24 months from the last dose of pembrolizumab.

Part 1 design and blinatumomab escalation/de-escalation rules

For part 1, subject enrollment will start in cohort Ia as outlined in the schema in Figure 1. Blinatumomab will be dosed as a continuous intravenous infusion (CIVI) for 8 weeks. The initial dose will be 9 µg/day and the dose will be escalated after 7 days to a target dose of 28 µg/day. Depending on tolerability, the target dose of blinatumomab will be increased to a maximum of 56 µg/day in cohort IIa, or to 112 µg/day in cohort IIIa. Pembrolizumab will be dosed by IV infusion 200 mg at Q3W starting on study day 15 in

cohort Ia, and on study day 19 in cohorts IIa and IIIa. Trial treatment of pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

Subjects who do not meet the criteria for investigational product discontinuation (see below) are eligible for a second cycle of blinatumomab (consolidation) consisting of a CIVI of 28 days after a 28-day (± 3 days) blinatumomab treatment-free interval. Blinatumomab will be started at 9 µg/day and escalated every 7 days to the maximum target dose of blinatumomab in the assigned cohort.

Subjects will be enrolled to part 1 with up to 6 subjects being enrolled per cohort. In any cohort, tolerability will be defined as ≤ 1 DLT out of 6 subjects. Expansion to 10 subjects will be allowed in any cohort to ensure adequate safety and PK data is collected. The decision to expand a cohort will be made by the DLRT. In case of 10 subjects enrolled, tolerability is defined as ≤ 2 DLTs out of 10 subjects.

The MTD of blinatumomab will be defined as the highest dose level at which at most 1 of 6 subjects or at most 2 subjects in 10 experiences a DLT. The MTD defines the stopping rules for the study. For further details on replacement of subjects, please see Section 3.4. For DLT criteria, please see Appendix E.

The DLRT will meet to review the safety data when any of the following criteria are met:

- In 2 or more subjects out of 6, a DLT has been reported, or in 3 or more subjects out of 10, a DLT has been reported in a cohort
- Six subjects are enrolled in a cohort and all subjects have completed the DLT observation period.
- In the event that a cohort is expanded to 10, DLRT will also meet after all subjects have completed DLT observation period.

The DLRT will review the available data in part 1 to determine if the combination of blinatumomab and pembrolizumab is safe and tolerable as defined by DLT criteria. Based on the totality of the data, the DLRT may recommend to declare MTD, to escalate to the next dose level, to expand a cohort to a maximum of 10 subjects if the collection of more data is deemed warranted, or to adjudicate the DLT criteria (see Appendix E for details). **At the end of Part 1, the cohort with recommended dose level requires to have at least 1 response out of 6 evaluable subjects or 2 responses out of 10 evaluable subjects to proceed to Part 2.**

Part 2

For part 2, the dosing will be determined based on the safety of the combination of blinatumomab and pembrolizumab and the MTD of blinatumomab established in part 1 per DLRT. For part 2, the DLT observation period will be determined by the cohort chosen in part 1 for the part 2 expansion. Part 2 will consist of an expansion cohort to collect further safety and PK data as well as provide a preliminary estimate of the efficacy of the combination of blinatumomab and pembrolizumab. Dose limiting toxicities **and efficacy** will be monitored **by the Data Review Team (DRT)** to ensure they do not reach a pre-defined threshold of 25%. If this threshold is reached, the **DRT** will have the discretion to change to another dose/schedule tested in phase 1b part 1 based on the totality of the available data. The details of DLT boundaries are provided in Section 10.3.1.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 35 sites located in (but not limited to) Australia, Europe, and North America will participate in this study. During the conduct of the study, additional regions, countries, or sites may be added as necessary.

Sites that do not enroll subjects **into an open cohort** within 6 months of site initiation may be **closed**.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. It is anticipated that a maximum of approximately **70** subjects will be enrolled into this study.

Please refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Part 1 subjects may be replaced if they are not evaluable for DLT, see Section 10.1.2.

All available safety data for subjects who are not DLT evaluable will be evaluated and considered in DLRT decisions.

Part 2 subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening for each subject will be up to 21 days. The duration of treatment will vary for each subject. Blinatumomab treatment will consist of an 8-week induction cycle and an optional 28-day consolidation cycle in those subjects who do not meet criteria for discontinuation after a 28-day (± 3 days) blinatumomab treatment-free interval for a total of 16 weeks. Pembrolizumab is continued until disease progression for a maximum of up to 35 cycles. For part 2, the dosing will be determined based on the safety of the combination of blinatumomab and pembrolizumab and the MTD of blinatumomab established in part 1 per DLRT. Part 2 will consist of an expansion cohort to collect further safety and PK data as well as provide a preliminary estimate of the efficacy of the combination of blinatumomab and pembrolizumab. Dose limiting toxicities **and efficacy** will be monitored **by the Data Review Team (DRT)** to ensure they do not reach a pre-defined threshold of 25%. If this threshold is reached, the **DRT** will have the discretion to change to another dose/schedule tested in phase 1b part 1 based on the totality of the available data. Subjects then enter the long-term follow-up period of the study following blinatumomab safety follow-up visit until approximately 24 months from the last dose of pembrolizumab.

The end of study for each subject is defined as the date the subject withdraws full consent from the study, completes the safety follow-up visit, or final long-term follow-up visit (whichever is later), or death.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up) as applicable.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must meet the following criteria:

101. Subject/legally acceptable representative has provided written informed consent prior to initiation of any study-specific procedures.
102. Age ≥ 18 years at the time of informed consent
103. Have histologically confirmed DLBCL that is either:
    - Refractory after at least one regimen of systemic chemotherapy and/or targeted therapy, **and refractory is defined as progressive or stable disease as the best response to the most recent systemic chemotherapy regimen or disease progression or relapse within 12 months after autologous stem cell transplantation; when using PET for assessment, for subjects with refractory disease and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy (Crump et al, 2017; Neelapu et al, 2017; Cheson et al, 2007),** or
    - In first or later relapse if have received at least 2 systemic regimens since time of diagnosis, or
    - Relapsed post-autologous or allogeneic HSCT with adequate organ function after proximity to transplantation time exclusions as specified in Exclusion Criteria 208 and 209
104. Have measurable disease defined as at least 1 lesion that can be accurately measured in at least 2 dimensions with spiral **computed tomography (**CT**)** scan. Minimum measurement must be either > 15 mm in the longest diameter OR > 10 mm in the short axis.
105. Demonstrate adequate organ function as defined in Table 4-1.

Table 4-1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500/mcL
Platelets	≥ 100, 000/mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Creatinine OR Measured or calculated[a] creatinine clearance (CrCl) (glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl)	≤ 1.5xULN OR ≥ 60 mL/min for subject with creatinine levels >1.5 x institutional upper limit of normal (ULN)
Hepatic	
Total bilirubin	≤ 1.5xULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5xULN OR ≤ 5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤ 1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SGOT = serum glutamic oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; ULN = upper limit of normal
[a] Creatinine clearance should be calculated per institutional standard.

106. Have resolution of toxic effect(s) of the most recent prior chemotherapy to grade 1 or less (except alopecia). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicities and/or complications of the intervention(s).

107. Female subjects of childbearing potential (Section 6.10.1) must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

108. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 6.10.1 for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

109. Male subjects must agree to use an adequate method of contraception as outlined in Section 6.10.2, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

110. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

111. Life expectancy of ≥ 12 weeks in the opinion of the Investigator

113. **Biopsy proven DLBCL (biopsy proven at least at primary diagnosis of DBLCL), including DLBCL that represents transformation of indolent NHL (including follicular, marginal zone, and lymphoplasmacytic lymphoma excluding chronic lymphocytic leukemia or Hodgkin Lymphoma) are eligible. Subjects with transformation of indolent lymphoma must have received therapy after a diagnosis of transformation that is appropriate for aggressive histology.**

4.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria will not be eligible to participate in this study:

201. Richter's transformation (DLBCL arising in the setting of prior chronic lymphocytic leukemia) or PMBCL

202. History or presence of clinically relevant CNS pathology such as epilepsy, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.

203. Has disease that is suitable for local therapy administered with curative intent.

204. Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s). Thirty days is calculated from day 1 of protocol-specified therapy

205. Has a diagnosis of immunodeficiency or has received systemic steroid therapy (in excess of 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of protocol specified therapy.

206. Has had a prior anticancer mAb within 30 days prior to first day of study treatment or who has not recovered (ie, ≤ grade 1 or at baseline) from adverse events due to such agents administered more than 30 days earlier.

207. Has had prior chemotherapy, targeted therapy, or radiation therapy within 14 days prior to first day of study treatment or who has not recovered (ie, ≤ grade 1 or at baseline) from adverse events due to such previously administered agents.

    Note: Subjects with ≤ grade 2 neuropathy or ≤ grade 2 alopecia are an exception to this criterion and may qualify for the study.

208. Has undergone prior allogeneic HSCT:
    - within the last 5 years

      OR
    - greater than 5 years ago but has active graft versus host disease (GvHD) requiring systemic treatment.

209. Has received autologous HSCT within 6 weeks prior to start of treatment.

211. History of other malignancy within the past 3 years with the exception of:
    - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated cervical carcinoma in situ without evidence of disease
    - Adequately treated breast ductal carcinoma in situ without evidence of disease
    - Prostatic intraepithelial neoplasia without evidence of prostate cancer
    - Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

212. Has known active CNS metastases and/or carcinomatous meningitis**; brain magnetic resonance imaging (MRI) is preferred for CNS disease assessment for all patients at screening; if MRI is contraindicated (eg, pacemaker, implant, et al) a CT can be performed.**

    Note: Subjects with previously treated CNS metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 28 days prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging CNS metastases, and are not using steroids for at least 7 days prior to protocol specified therapy. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

213. Has active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

    Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

214. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

215. Has a history of interstitial lung disease

216. Has an uncontrolled active infection requiring systemic therapy

217. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

218. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the subject has previously participated in Merck MK-3475 (pembrolizumab) clinical trials.
219. Has received prior anti-CD19 directed therapy.
220. Known hypersensitivity to Igs or any other component of the study drugs formulation.
221. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
222. Has chronic or active Hepatitis B (eg, hepatitis b surface [HBs] antigen reactive or quantifiable hepatitis b virus [HBV] viral load) or Hepatitis C (eg, hepatitis c virus [HCV] RNA [qualitative] is detected).
224. Has received a live vaccine within 30 days of planned start of protocol specified therapy.
225. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and/or investigator's knowledge.
226. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
227. Has a history of solid organ transplantation.
228. **Biopsy proven DLBCL with substantial occurrence of malignant cells into the bloodstream (lymphocyte count ≥ 7 x 10^9/L) including all leukemic presentations, even though with acceptable histologies.**

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects or legally acceptable representatives must personally sign and date the ICF before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and Amgen confirms the enrollment. The investigator is to document this decision and date in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (entry is defined as the point at which the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. This number will be used to

identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects who are unable to complete or meet eligibility at the initial screening will be permitted to re-screen twice. Re-screen subjects must first be registered as a screen failure manually and subsequently registered as re-screen. Once the subject is registered as re-screened, a new 21 day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening.

Subjects re-screening within 21 days of the signing of the original informed consent only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. Subjects re-screening greater than 21 days from the signing of the original informed consent must be re-consented and repeat all screening procedures per the protocol.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Subjects should initiate protocol-specified therapy within 5 days of enrollment confirmation.

6. TREATMENT PROCEDURES

The investigational products for this study are blinatumomab and pembrolizumab. Blinatumomab will be manufactured and packaged by Amgen, Inc. and distributed using Amgen clinical study drug distribution procedures. Pembrolizumab will be labeled, packaged, and distributed by Amgen (or designee) using Amgen (or designee) clinical study drug distribution procedures. Pembrolizumab is supplied as pembrolizumab 100 mg/4 mL vials (25 mg/mL) solution for IV infusion. Additional details regarding the pembrolizumab product are provided in the investigational product instruction manual (IPIM).

The term protocol-specified therapies used throughout the protocol refers to blinatumomab and pembrolizumab. It does not refer to other protocol-mandated medication (eg, pre-phase treatment with dexamethasone or intrathecal prophylaxis).

All other protocol-mandated therapies, including pre-phase therapies, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-mandated therapies.

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen investigational product used in this study is blinatumomab.

The non-Amgen investigational product used in this study is pembrolizumab.

The IPIM, a document external to this protocol, containing detailed information regarding the storage, preparation, and administration of blinatumomab and pembrolizumab will be provided to each investigational site.

Non-investigational medical device(s) (ie, medical device(s) not under study) or products will be described in Section 6.7.

6.2 Investigational Product

6.2.1 Amgen Investigational Product: Blinatumomab

Blinatumomab will be supplied as 4 mL single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for IV infusion following reconstitution with sterile water for injection. Sterile water for injection and supplies required for reconstitution and injection of blinatumomab will not be provided to clinical sites.

To prepare blinatumomab for CIVI, the lyophilized powder is reconstituted with sterile water for injection. The reconstituted solution is added to an infusion bag containing 0.9% NaCl and a product-specific stabilizer (IV Solution Stabilizer). The IV solution stabilizer functions to prevent adsorption of blinatumomab to surfaces of the infusion components. The IV Solution Stabilizer is supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate.

For information surrounding the use of a continuous infusion pump, refer to Section 6.7.

6.2.1.1 Blinatumomab Dosage, Administration, and Schedule

Blinatumomab is administered as a CIVI. The infusion bags will be changed by site nursing or home health care personnel trained on the protocol and on the proper administration of blinatumomab.

The first cycle of blinatumomab treatment **consists of** 8 weeks **(56 days) of standard blinatumomab continuous infusion**. Please refer to the study schema (Figure 1).

The first cycle is followed by a 28-day (± 3 days) blinatumomab treatment-free interval. Those subjects who do not meet criteria for discontinuation after the blinatumomab treatment-free interval may then receive a consolidation cycle of blinatumomab (cycle 2) **consisting** of 28 days **standard blinatumomab continuous infusion**. In both cycle 1

and the consolidation cycle, the initial dose of blinatumomab will be 9 µg/day and will be dose escalated at 7-day intervals until the target dose is reached.

The dosing and schedule will be as outlined in Section 7.

The drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible and the infusion restarted at the earliest time possible. Every interruption longer than 1 hour should be documented. Administration of dexamethasone premedication will occur as described in Section 6.3. I**n case** the infusion is interrupted **in the first cycle and/or the second cycle**, the total **days at the target dose** should **be at least 85% of the planned days, but no more than the planned days**.

A dose of up to 10% higher than the intended blinatumomab dose (per day) may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject is stabilized and no clinically relevant safety findings due to blinatumomab are observed, resumption of blinatumomab at a correct dose can be considered after consultation with the Amgen medical monitor.

For blinatumomab, a dose of greater than 10% higher than the intended dose will be considered clinically important and classified as a serious adverse event under the criterion of “other medically important serious event” per Section 9.1.3. If the overdose results in additional adverse event/s, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s should be recorded/reported per Section 9.2 of the protocol.

The dose, start and stop date/time, and lot number of protocol-specified therapy is to be recorded on each subject’s CRF.

Refer to the Blinatumomab Investigational Brochure for further information.

6.2.1.2 Blinatumomab Inpatient Dosing

Subjects are required to be monitored in a hospital for a minimum of 72 hours following initiation of therapy and for a minimum of 48 hours at each step dose increase. Close monitoring is indicated because of the potential adverse events associated with T cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses/physicians familiar with such conditions should be available for immediate intervention in case of complications.

Also, if blinatumomab is interrupted for longer than 4 hours, re-start of the infusion should be performed in the hospital, under the supervision of the investigator. The subject should be observed overnight for possible side effects after the re-start, either in the hospital or in the outpatient setting as applicable. Administration of dexamethasone premedication will occur as described in Section 6.3.

6.2.1.3 Blinatumomab Outpatient Dosing

Apart from the situations where inpatient dosing is required per Section 6.2.1.2, and if a subject is deemed stable by the investigator, blinatumomab infusion may continue as an outpatient. Twenty-four-hour emergency on-call service must be ensured in the outpatient setting.

In the outpatient setting, either the subject will return to the study site for changes of infusion bags or the subject will be visited by a well-trained ambulant/home care service provider at specific intervals to change the infusion bag. The subject and the ambulant/home care provider will be trained and will receive written instructions for storage of the IV bags.

For the ambulant/home care provider study-specific requirements and recording of source documentation must be completed before any study-related tasks are started. The date and time of infusion bag changes, all infusion start and stop times, and any dose modifications should be recorded accurately.

A comprehensive list of all home care services, including but not limited to the storage, handling, and administration of blinatumomab as well as mandatory procedural and data collection requirements will be separately provided in a home health care manual.

Following each visit, this information will be documented on the Ambulant/Home Care Services visit worksheet and forwarded to the investigator. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. The ambulant/home care professionals must provide 24-hour emergency on-call service. In addition, the subject will visit the study site for the examinations according to the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4).

6.2.1.4 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation for Blinatumomab

6.2.1.4.1 Infusion Interruption/Dose Modification Due to Adverse Events for Blinatumomab

Common Terminology Criteria for Adverse Events (CTCAE v 4.0) grade 4 adverse events at least possibly related to blinatumomab will require that the administration of

blinatumomab be stopped until the adverse event has recovered to CTCAE grade 1 or baseline.

Table 6-1. Blinatumomab Discontinuation and Stopping Rules

Toxicity	Grade	Instructions for Treatment Interruption and Re-start
Cytokine Release Syndrome (CRS)	3	•Interrupt blinatumomab until the event improves to grade ≤ 1 and administer corticosteroids (refer to Table 6-4) •Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: ○If the event occurred at 56 or 112 µg/day, resume at 28 µg/day ○If the event occurred at 28 µg/day, resume at 9 µg/day •Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of cohort (28 µg/day for cohort Ia, 56 µg/day for cohort IIa, 112 µg/day for cohort IIIa) if toxicity does not reoccur. •Permanently discontinue if: ○Initial grade 3 CRS does not improve to grade ≤ 1 within 7 days, OR ○Grade 3 CRS reoccurs at the lower dose level within 7 days of re-initiation OR ○Grade 3 CRS reoccurs at a dose of 9µg/day without prior step-dose escalation.
	4	•Permanently discontinue blinatumomab
Neurologic Events	3	•Interrupt blinatumomab until the event improves to grade ≤ 1 and administer corticosteroids (refer to Table 6-4) •Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: ○If the event occurred at 56 or 112 µg/day, resume at 28 µg/day ○If the event occurred at 28 µg/day, resume at 9 µg/day •Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of cohort (28 µg/day for cohort Ia, 56 µg/day for cohort IIa, 112 µg/day for cohort IIIa) if toxicity does not reoccur. •Permanently discontinue if: ○Initial grade 3 neurologic event occurred at 9 µg/day, OR ○Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days, OR ○Grade 3 neurologic event reoccurs at the lower dose level within 7 days of re-initiation, OR ○Grade 3 neurologic event reoccurs at a dose of 9 µg/day
	4	•Permanently discontinue blinatumomab
	Seizure[a] Grade ≥ 2	•Interrupt blinatumomab, administer corticosteroids (refer to Table 6-4) and anti-seizure medication per local practice •For restart, refer to grade 3 neurologic events above for dose level rules for re-instituting infusion •Do not re-initiate blinatumomab until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved and documented •Permanently discontinue if a second seizure occurs with re-initiation of blinatumomab at any dose

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Footnotes defined on the next page of the table

Table 6-1. Blinatumomab Discontinuation and Stopping Rules

Toxicity	Grade	Instructions for Treatment Interruption and Re-start
Elevated Liver Enzymes		•Interrupt blinatumomab if any one of the following occurs: ○TBL > 3 x ULN at any time ○ALP > 8 x ULN at any time ○AST or ALT > 8 x ULN at any time ○AST or ALT > 5 x ULN but < 8 x ULN for ≥ 14 days ○AST or ALT > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (eg, right upper quadrant abdominal pain/tenderness, fever, nausea, vomiting, jaundice) •Permanently discontinue blinatumomab if: ○TBL > 2 x ULN OR INR >1.5 (for subjects not on anticoagulant therapy) AND ○AST or ALT > 3x ULN (when baseline was <ULN) AND ○no other cause for the combination of the above laboratory abnormalities is immediately apparent •Refer to Section 6.4 for additional detail
Other Clinically Relevant Adverse Events	3	•Interrupt blinatumomab until event improves to grade ≤1 •Restart no less than 72 hours after the initial observation of the grade 3 event at the following dose levels: ○If event occurred at 56 or 112 µg/day, resume at 28 µg/day ○If event occurred at 28 µg/day, resume at 9 µg/day •Escalate up 1 dose level after 7 days if toxicity does not reoccur. Increase dose stepwise at 7-day intervals to target dose of cohort (28 µg/day for cohort Ia, 56 µg/day for cohort IIa, 112 µg/day for cohort IIIa) if toxicity does not reoccur. •Permanently discontinue blinatumomab if: ○Initial grade 3 event does not improve to grade ≤ 1 within 14 days, (with the exception of delay in restart due to logistical difficulties, in which case the restart may be postponed for an additional 7 days) OR ○Grade 3 event reoccurs at the lower dose level within 7 days of re-initiation, OR ○Grade 3 event reoccurs at a dose of 9 µg/day without prior step-dose escalation
	4	•Permanently discontinue blinatumomab

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ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; MRI = magnetic resonance imaging; TBL = total bilirubin; ULN = upper limit of normal

[a] Obtain brain MRI and perform cerebrospinal fluid (CSF) analysis, if there are no contraindications.

Subjects who have been dose reduced will have an option to re-escalate to higher dose levels within their assigned dose cohort once the adverse event has resolved to grade 1 or less for at least 7 days. (See Appendix F).

Re-start of the infusion should be performed in the hospital, under supervision of the investigator. Before blinatumomab is re-started, premedication with dexamethasone must be administered as described in Table 6-4. The subject should be observed over night for possible side effects after each restart, either in the hospital or in the outpatient setting, as applicable. **When the blinatumomab infusion is re-started per Table 6-1 guidelines, the schedule of assessment procedures should be repeated to align with the re-started blinatumomab dose. If re-start is at 9 µg/d then repeat schedule of assessments starting at D1. If re-start is at 28 µg/d then repeat schedule of assessments starting at D8. Refer to Table 7-1 and Table 7-2 for cohort Ia and Table 7-3 and Table 7-4 for cohort IIa/IIIa. In addition, at the start of blinatumomab cycle 2, subjects should resume the schedule of assessments following D85 to D110 procedures as outlined in Table 7-1 for cohort Ia and Table 7-3 for cohort IIa/IIIa (exception is for pembrolizumab specific tests which are referenced in Table 7-2 and Table 7-4).**

In addition to the events described above, the dose may be temporarily or permanently reduced if, by investigator´s judgment, it is necessary for safety reasons.

After at least 7 days of dosing at the reduced level, the dose may be increased back to the next higher dose level. An infusion interruption of more than 14 days due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. In case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation. Treatment may be also interrupted or permanently discontinued at the discretion of the investigator if any clinical/laboratory adverse event is considered to be medically relevant.

In case of signs of cytokine release, dexamethasone must be administered orally or IV at a dose of at maximum 3 x 8 mg/day for up to 72 hours.

6.2.2 Non-Amgen Investigational Product: Pembrolizumab

The non-Amgen investigational product pembrolizumab will also be used in this study.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

Additional details regarding the product(s) are provided in the IPIM.

6.2.2.1 Pembrolizumab Dosage, Administration, and Schedule

Trial treatment should begin as close as possible to the date on which the subject is allocated/assigned. The pembrolizumab treatment to be used in this trial is outlined below in Table 6-2.

Schedule of pembrolizumab dosing and related assessments for cohort Ia are provided in Table 7-1 and Table 7-2, and for cohorts IIa and IIIa are provided in Table 7-3 and Table 7-4. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between - 5 minutes and + 10 minutes is permitted (ie, infusion time is 30 minutes - 5 minutes/+ 10 minutes).

For this trial, an overdose of pembrolizumab will be defined as ≥ 1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose of pembrolizumab, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Table 6-2. Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Maximum Length of Dosing	Route of Administration	Regimen[a]	Use
Pembrolizumab	200 mg	Every 21 days	Up to 35 cycles	Intravenous	**First dose s**tarting at study day 15 (cohort Ia), and study day 19 (cohorts IIa and IIIa) (21-day cycles)	Experimental

[a] **Starting from p**embrolizumab **cycle 2, pembrolizumab** may be administered **±** 3 days **from the planned dosing day**.

6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation for Pembrolizumab

6.2.2.2.1 Dose modification of Pembrolizumab if Blinatumomab has been interrupted

If toxicities due to blinatumomab do not resolve to grade ≤ 1 within 7 days of treatment interruption and supportive care as outlined, pembrolizumab will also be interrupted until both may be resumed per protocol.

The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1). The first dose of

pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events, no > grade 1 CRS and/or neurologic events.

6.2.2.2.2 Dose Modification and Toxicity Management for Immune-related Adverse Events Associated With Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an **immune-related response**. These immune-related adverse events (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs **were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs ensure** adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6-3.

Table 6-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:

1. **S**evere and life-threatening irAEs **should be treated with** IV corticosteroid**s** followed by oral steroid**s**. Other immunosuppressive treatment should be**gin** if **the** irAEs **are not** be controlled by corticosteroids.
2. **Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment.**
3. **The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.**
4. **If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.**

irAEs	Toxicity grade (CTCAE v**5**.0)	Action **with** pembrolizumab	**C**orticosteroid and/or other therapies	Monitor**ing** and follow-up
Pneumonitis	Grade 2	Withhold	•Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper •**Add prophylactic antibiotics for opportunistic infections**	•Monitor participants for signs and symptoms of pneumonitis •Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	•Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	•Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). •Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. •Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Footnotes defined on last page table

Table 6-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:

1. **S**evere and life-threatening irAEs **should be treated with** IV corticosteroid**s** followed by oral steroid**s**. Other immunosuppressive treatment should be**gin** if **the** irAEs **are not** be controlled by corticosteroids.
2. **Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment.**
3. **The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.**
4. **If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.**

irAEs	Toxicity grade (CTCAE v**5**.0)	Action **with** pembrolizumab	**C**orticosteroid and/or other therapies	Monitor**ing** and follow-up
AST **or** ALT elevation or Increased **B**ilirubin	Grade 2[a]	Withhold	•Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	•Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[b] or 4[c]	Permanently discontinue	•Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	•Initiate insulin replacement therapy for participants with T1DM •Administer anti-hyperglycemic in participants with hyperglycemia	•Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	•Administer corticosteroids and initiate hormonal replacements as clinically indicated.	•Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		

Footnotes defined on last page table

Table 6-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:

1. **S**evere and life-threatening irAEs **should be treated with** IV corticosteroid**s** followed by oral steroid**s**. Other immunosuppressive treatment should be**gin** if **the** irAEs **are not** be controlled by corticosteroids.
2. **Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment.**
3. **The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.**
4. **If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.**

irAEs	Toxicity grade or conditions (CTCAE v**5**.0)	Action **with** pembrolizumab	**C**orticosteroid and/or other therapies	Monitor**ing** and follow-up
Hyperthyroidism	Grade 2	Continue	•Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	•Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2**, 3,** 4	Continue	•Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	•Monitor for signs and symptoms of thyroid disorders.
Nephritis**: grading according to increased creatinine or acute kidney injury**	Grade 2	Withhold	•Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	•Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	•Based on severity of AE administer corticosteroids	•Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Footnotes defined on last page table

Table 6-3. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:

1. **S**evere and life-threatening irAEs **should be treated with** IV corticosteroid**s** followed by oral steroid**s**. Other immunosuppressive treatment should be**gin** if **the** irAEs **are not** be controlled by corticosteroids.
2. **Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last pembrolizumab treatment.**
3. **The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.**
4. **If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.**

irAEs	Toxicity grade or conditions (CTCAE v**5**.0)	Action **with** pembrolizumab	**C**orticosteroid and/or other therapies	Monitor**ing** and follow-up
All **O**ther immune-related AEs	**P**ersistent Grade 2	Withhold	•Based on severity of AE administer corticosteroids	•Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; **ULN = upper limit of normal**

[a] **AST/ALT: > 3.0 - 5.0 x ULN, if baseline normal; > 3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN, if baseline normal; > 1.5 to 3.0 x baseline, if baseline abnormal**

[b] **AST/ALT: > 5.0 to 20.0 x ULN, if baseline normal; > 5.0 - 20.0 x baseline, if baseline abnormal; bilirubin: > 3.0 - 10.0 x ULN, if baseline normal; > 3.0-10.0 x baseline, if baseline abnormal**

[c] **AST/ALT: > 20.0 x ULN, if baseline normal; > 20.0 x baseline, if baseline abnormal; bilirubin: > 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal**

[d] **The decision to w**ithhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **If control achieved or < Grade 2, pembrolizumab may be resumed.**

[e] **Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.**

6.2.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation of Protocol Specified Therapy

Treatment with protocol specified therapy should be discontinued in the event of any of the following:

- Documented disease progression per **the Lugano Classification** (Cheson et al, **2014**) **and Revised Response Criteria (Cheson et al, 2007)** at any time following the first (8 week) cycle of blinatumomab.

  After the first documentation of progression, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed 4 to 8 weeks from initial assessment suspicious for PD for subjects meeting criteria in Section 7.3.12. The first documented progression will still be counted as a progression event.
- Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol-specified safety criteria or desirable in the investigator's and/or the subjects opinion
- Investigator's decision that a change of therapy is in the subject's best interest
- Administration of relevant non-permitted concomitant medications
- Investigator's decision that a subject does not benefit from treatment anymore, eg, non-response or development of progressive disease
- Intercurrent medical condition, which in the opinion of the investigator or the subject precludes further treatment of the subject
- Withdrawal of subject's consent to study treatment

6.3 Dexamethasone Premedication

Mandatory premedication with dexamethasone is required. Refer to Table 6-4 for details.

Table 6-4. Dexamethasone Predose Treatment and for Events

Treatment Phase	Target Subjects:	Dexamethasone Dose
Pre-dose Dexamethasone Prior to Each Blinatumomab Treatment Cycle and Before Each Dose Step Increase	All subjects	Dexamethasone 20 mg IV: within 6 hours prior to start of treatment in each treatment cycle, and within 6 hours prior to dose step (increase).
Infusion Interruption/Dose Modification Due to Adverse Event or Interruption due to Technical/Logistical Event	Subjects who interrupt treatment > 4 hours	Dexamethasone 20 mg IV: within 6 hours prior to re-start of treatment
In case of signs of CRS	Subjects with signs of CRS	Dexamethasone orally or IV at a dose maximum of 3 doses of 8 mg/day (24 mg/day) for up to 72 hours. The dose should then be reduced step-wise over 4 days.
Infusion Interruption/Dose Modification Due to Neurologic Events	Subjects with neurologic event	Dexamethasone should be administered at a dose of at least 24 mg/day for up to 72 hours. Dexamethasone will then be reduced step-wise over 4 days.

CRS = cytokine release syndrome; IV = intravenous

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.4.1 Criteria for Withholding and/or Permanent Discontinuation of Blinatumomab and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
- Right sided heart failure, hypotension or any other cause of hypoxia, congestion, and/or ischemia to the liver.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)
- Cytokine release syndrome

If investigational product(s) is/are withheld, the subject is to be followed according to recommendations in Appendix A for possible drug-induced liver injury (DILI).

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.2).

Refer to Table 6-3 for pembrolizumab dose modifications.

Table 6-5. Conditions for Withholding and/or Permanent Discontinuation of Blinatumomab Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x upper limit of normal (ULN) at any time	> 2x ULN
		OR
INR	--	> 1.5 (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 14 days > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).	No other cause for the combination of the above laboratory abnormalities is immediately apparent > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alkaline aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin

6.4.2 Criteria for Rechallenge of Blinatumomab After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then blinatumomab as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 6-5) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious adverse events and ECIs (Events of Clinical Interest) as defined in Section 9.1.4.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medications will be recorded on the electronic case report form (eCRF) including all prescriptions, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, routes, and start and end dates should also be included on the eCRF.

Recording of concomitant medication during long-term follow-up period is limited to only anti-lymphoma treatments.

6.6 Other Treatment Procedures

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication**s** will be recorded on the CRF including all prescriptions, OTC products, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

6.7 Medical Devices

Blinatumomab must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment. Blinatumomab infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines that are both compatible with the investigational product as described in the IPIM. The blinatumomab final solution for infusion should not come into contact with the pump at any time.

Additional details for the use of the above mentioned medical devices are provided in the IPIM.

6.8 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.9 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase with protocol specified therapy (including retreatment for post-complete remission relapse) of this trial:

- antineoplastic systemic chemotherapy or biological therapy
- immunotherapy not specified in this protocol
- chemotherapy not specified in this protocol
- investigational agents other than blinatumomab and pembrolizumab within 30 days prior to the start of protocol specified therapy
- radiation therapy

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with the sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days prior to the start of protocol specified therapy and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG (Bacillus Calmette-Guérin), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids or other immunosuppressants for any purpose other than those which are protocol mandated or given as treatment for an adverse event.

  Note: Inhaled steroids are allowed for management of asthma or chronic obstructive pulmonary disease (COPD).

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from protocol specified therapy but will continue to be followed on the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

For other medications that are prohibited in this trial, refer to exclusion criteria in Section 4.2.

If a subject starts a new anti-lymphoma treatment within 30 (± 3) days of their last dose of protocol-assigned therapy, a safety follow-up visit should be conducted immediately prior to starting any new treatment, including HSCT conditioning regimens.

6.10 Contraceptive Requirements

6.10.1 Female Subjects

Female subjects of childbearing potential must agree to practice true sexual abstinence (refrain from sexual intercourse) or use an acceptable method of effective birth control during treatment and for an additional 120 days after the last dose of study drug.

Acceptable methods of effective contraception include: Hormonal (Combined estrogen and progestogen or progesterone-only hormonal contraception given via oral, intravaginal, transdermal, injectable, or implantable route); intrauterine device (IUD); intrauterine hormonal-releasing system (IUS); Bilateral tubal occlusion/ligation; Vasectomized partner (provided that partner is the sole sexual partner of the female participant who is of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success); Two barrier methods (one by each partner) and the female partner must use spermicide (if spermicide is commercially available) with the barrier method (the male must use a condom [latex or other synthetic material]) and the female may select either a diaphragm, cervical cap or contraceptive sponge. A female condom is not an option because there is a risk of tearing when both partners use a condom. The reliability of true sexual abstinence must be evaluated by the investigator and be the preferred and usual lifestyle of the subject.

Females not of childbearing potential are defined as: Any female who has undergone a total hysterectomy, and/OR bilateral salpingectomy, and/OR bilateral oophorectomy, OR bilateral tubal ligation, OR is postmenopausal. Postmenopausal women are:

- Age > 55 years with cessation of menses for 12 or more months
- Age < 55 years but no spontaneous menses for at least 2 years
- Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with follicle-stimulating hormone levels > 40 IU/L, or postmenopausal estradiol levels < 5 ng/dL, or according to the definition of "postmenopausal range" for the laboratory involved.

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period and for 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.10.2 Male Subjects

Male subjects of reproductive potential must agree to avoid impregnating a partner while receiving study drug and for 120 days after the last dose of study drug.

6.10.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with study drug, the subject will immediately be discontinued from study treatment and will continue on the study for long-term follow-up. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor.

6.10.4 Use in Nursing Women

It is unknown whether blinatumomab or pembrolizumab are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment. Women should not breastfeed within 120 days after the last dose of pembrolizumab and 48 hours after the last dose of blinatumomab.

6.10.5 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Refer to the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4) for an outline of the procedures required at each visit.

Table 7-1. Schedule of Assessments for Cohort Ia (And for Part 2 if MTD is Reached in Cohort Ia)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 – 57) Blinatumomab Infusion Cycle 2 (Days 85- 113) Blinatumomab Infusion													Blinatumomab Treatment Free Period (Days 58-84)		Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 - 3													Pembrolizumab Cycle 4		30 days (+7 days) after last dose	Every 12 weeks (±28 days)
		Pembrolizumab Cycle 5 [After cycle 5: continued Pembrolizumab cycles every 21 days (Table 7-2)]																
Day (D)	D-20 to D0	D1[b,II]	D2	D3	D8[II]	D10	D15	D16	D22	D29	D36	D43	D50	D57	D64	D78		
Day (D)		D85	D86	D87	D92	D94	D99	D100	D106	D113								
Protocol-Required Therapy Administration																		
Blinatumomab[c]		X	X	X	X	X	X	X	X	X	X	X	X	X				
Pembrolizumab[d]							X				X			X		X		
General Assessments																		
Informed Consent	X																	
Inclusion/ Exclusion Criteria	X																	
Demographics	X																	
Medical History/Current Medical Condition	X																	

Footnotes defined on the last page of the table

Table 7-1. Schedule of Assessments for Cohort Ia
(And for Part 2 if MTD is Reached in Cohort Ia)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 – 57) Blinatumomab Infusion Cycle 2 (Days 85- 113) Blinatumomab Infusion													Blinatumomab Treatment Free Period (Days 58-84)		Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 - 3 Pembrolizumab Cycle 5 [After cycle 5: continued Pembrolizumab cycles every 21 days (Table 7-2)]													Pembrolizumab Cycle 4		30 days (+7 days) after last dose	Every 12 weeks (±28 days)
Day (D)	D-20 to D0	D1[b,II]	D2	D3	D8[II]	D10	D15	D16	D22	D29	D36	D43	D50	D57	D64	D78		
Day (D)		D85	D86	D87	D92	D94	D99	D100	D106	D113								
General Assessments (continued)																		
ECOG Performance Status	X																X	
Vital signs	X	X[e]	X	X	X[e]	X	X		X	X	X	X	X	X			X	
Physical Examination (including neurological examination)	X	X			X		X		X	X	X	X	X	X			X	
Height & Weight[f]	X	X															X	
Concomitant Medication	X	Continuously throughout the study																X[g]
AE/SAE Assessment	X[h]	Continuously throughout the study																X[h]

Footnotes defined on the last page of the table

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Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 – 57) Blinatumomab Infusion Cycle 2 (Days 85- 113) Blinatumomab Infusion													Blinatumomab Treatment Free Period (Days 58-84)		Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 - 3 Pembrolizumab Cycle 5 [After cycle 5: continued Pembrolizumab cycles every 21 days (Table 7-2)]													Pembrolizumab Cycle 4		30 days (+7 days) after last dose	Every 12 weeks (±28 days)
Day (D)	D-20 to D0	D1[b,ll]	D2	D3	D8[ll]	D10	D15	D16	D22	D29	D36	D43	D50	D57	D64	D78		
Day (D)		D85	D86	D87	D92	D94	D99	D100	D106	D113								
General Assessments (continued)																		
Disease Related Events		Continuously throughout the study																
Radiologic Assessments																		
Brain MRI[i]	X																	
CT scan[j,k,l]	X[m,n]														X[l,n]			X[l,n]
PET scan[j,l]	X[m]														X[l,o]			X[l,o]
Local Laboratory Tests																		
Bone Marrow Biopsy[p,q]	X														X[r]			X[r]

Footnotes defined on the last page of the table

Table 7-1. Schedule of Assessments for Cohort Ia (And for Part 2 if MTD is Reached in Cohort Ia)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 – 57) Blinatumomab Infusion Cycle 2 (Days 85- 113) Blinatumomab Infusion													Blinatumomab Treatment Free Period (Days 58-84)		Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 - 3 Pembrolizumab Cycle 5 [After cycle 5: continued Pembrolizumab cycles every 21 days (Table 7-2)]													Pembrolizumab Cycle 4		30 days (+7 days) after last dose	Every 12 weeks (±28 days)
Day (D)	D-20 to D0	D1[b,ll]	D2	D3	D8[ll]	D10	D15	D16	D22	D29	D36	D43	D50	D57	D64	D78		
Day (D)		D85	D86	D87	D92	D94	D99	D100	D106	D113								
Local Laboratory Tests (continued)																		
Lumbar Puncture[p]	X																	
Chemistry[s]	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	
Coagulation	X	X	X	X	X	X	X		X	X	X	X	X				X	
Hematology/CBC[s]	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	
Immunoglobulins (IgG)		X[t]										X			X		X	
Urinalysis[s]	X						X							X			X	
Creatinine Clearance	X																	
Thyroid function tests[s,u]	X						X							X			X[v]	

Footnotes defined on the last page of the table

Table 7-1. Schedule of Assessments for Cohort Ia
(And for Part 2 if MTD is Reached in Cohort Ia)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 – 57) Blinatumomab Infusion Cycle 2 (Days 85- 113) Blinatumomab Infusion													Blinatumomab Treatment Free Period (Days 58-84)		Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 - 3													Pembrolizumab Cycle 4		30 days (+7 days) after last dose	Every 12 weeks (±28 days)
		Pembrolizumab Cycle 5 [After cycle 5: continued Pembrolizumab cycles every 21 days (Table 7-2)]																
Day (D)	D-20 to D0	D1[b,ll]	D2	D3	D8[ll]	D10	D15	D16	D22	D29	D36	D43	D50	D57	D64	D78		
Day (D)		D85	D86	D87	D92	D94	D99	D100	D106	D113								
Local Laboratory Tests (continued)																		
HBsAg, anti-HBc, anti-HBs (screening only) and HBV viral load[w]	X	X[x]			X		X		X	X	X	X	X	X	X	X		
Pregnancy Test[y]	X																	
Central Laboratory Tests																		
Anti-Blinatumomab antibodies[z]		X										X					X[aa]	
Anti-Pembrolizumab antibodies[s,bb]							X[cc]				X					X	X[v]	
Immune panel[dd,ee]		X	X	X	X	X			X			X			X			

Footnotes defined on the last page of the table

Table 7-1. Schedule of Assessments for Cohort Ia
(And for Part 2 if MTD is Reached in Cohort Ia)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 – 57) Blinatumomab Infusion Cycle 2 (Days 85- 113) Blinatumomab Infusion													Blinatumomab Treatment Free Period (Days 58-84)		Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 - 3 Pembrolizumab Cycle 5 [After cycle 5: continued Pembrolizumab cycles every 21 days (Table 7-2)]													Pembrolizumab Cycle 4		30 days (+7 days) after last dose	Every 12 weeks (±28 days)
Day (D)	D-20 to D0	D1[b,ll]	D2	D3	D8[ll]	D10	D15	D16	D22	D29	D36	D43	D50	D57	D64	D78		
Day (D)		D85	D86	D87	D92	D94	D99	D100	D106	D113								
Central Laboratory Tests (continued)																		
Serum cytokines[ff, ii]		X	X	X	X		X		X									
PK Sample (Blinatumomab)[gg]		X	X		X	X	X		X	X		X						
PK Sample predose (Pembrolizumab)[s,hh, ii]							X[cc]				X					X		
PK Sample postdose (Pembrolizumab)[s,ii, jj]							X	X	X	X							X[v]	
Core or incisional/excisional biopsy for biomarker analysis	X[kk]														X[kk]			
MRD by NGS	X														X			

AE = adverse event; CBC = complete blood count; CNS = central nervous system; CR = complete remission; **CRS = cytokine release syndrome;** CSF = cerebrospinal fluid; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; FU = follow up; HBc = hepatitis b core; HBs = hepatitis b surface; HBsAg = hepatitis b surface antigen; HBV = hepatitis b virus; HSCT = hematopoietic stem cell transplantation; IV = intravenous; LTFU = long-term follow-up; MRD = minimal residual disease; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NGS = next generation sequencing; PET = positron emission tomography; PK = pharmacokinetics; SAE = serious adverse event

[a] Safety follow-up will occur 30 days (+7 days) after last dose of each protocol specified therapy. If a subject starts a new anti-lymphoma treatment within 30 (± 3) days of their last dose of protocol-assigned therapy, a safety follow-up visit should be conducted immediately prior to starting any new treatment, including HSCT conditioning regimens.

[b] All procedures completed on first day of study treatment must be completed prior to the initiation of protocol-required therapy. Subjects should initiate protocol-specified therapy within 5 days of enrollment confirmation.

[c] The initial dose of blinatumomab will be 9 µg/day and the dose will be escalated at weekly intervals until the target dose is reached. See Figure 1. **For subjects that experience a blinatumomab dose interruption during cycle 1, subjects should resume the schedule of assessments following D85-110 procedures on Table 7-3 at the start of cycle 2.**

[d] Pembrolizumab will be administered starting on study day 15 (21-day cycles). See Section 6.2.2. Pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards. For pembrolizumab dosing past cycle 5, see Table 7-2.

[e] Vital signs should be monitored continuously every 4 hours during the first 12 hours after the start of each new treatment/dose step.

[f] Height to be measured at screening only. Weight to be measured at screening, baseline, and safety follow-up visit.

[g] Recording of concomitant medication documentation during follow-up period is limited to only anti-lymphoma treatments.

[h] Report AEs occurring after enrollment only, and SAEs that occur after signing of the informed consent form. During long-term follow-up, any SAE that is determined to be related to protocol-required therapy should be reported.

[i] Available results of brain contrast-enhanced MRI performed up to 8 weeks prior to first day of study treatment are acceptable. In case of neurologic AE ≥ grade 3 a brain MRI should be performed.

[j] If PET scans and CT scans are done separately, they must be within the ± 3 day window and a maximum of 72 hours apart. If PET and CT are acquired on the same day, it is strongly recommended that PET is performed prior to the CT with IV contrast.

[k] Enhanced MRI will be allowed to replace CT strictly when iodinated contrast is contraindicated.

[l] After week 10 and during LTFU, subjects should have scans performed per the regular frequency every 12 weeks (± 3 days). PET/**CT**s should be performed until documented complete remission, progressive disease, or 24 months after the first assessment. Response assessment will also be conducted at the time of treatment discontinuation due to clinically suspected disease progression. In case of suspected pseudo-progression, repeat imaging performed 4 to 8 weeks from initial assessment suspicious for PD. Subjects who receive at least 1 full dose of pembrolizumab who discontinue from all study treatment in cycle 1, for whatever reason, shall undergo a PET/CT scan between 14 to 28 days after last pembrolizumab exposure.[m] Scans done within 28 days prior to first dose may be used in place of protocol-required assessments.

[n] If PET scan at Screening is negative for disease involvement in the neck, screening and subsequent CT scans may not include neck. If PET scan at Screening is positive for disease involvement of the neck, subsequent CT scans must include neck.

[o] For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in follow-up assessments.

[p] Lumbar puncture and bone marrow biopsy performed up to 49 days prior to enrollment may be used in place of protocol-required assessments. An assessment of the CSF will be performed at screening if there is a concern of CNS lymphoma involvement or during treatment period if subject has a seizure. Cerebrospinal fluid, cell count, glucose, and protein will be measured at the local laboratory as part of the examination to ensure that no infiltration of the CSF by DLBCL is present. Additional investigations of the CSF should be performed as clinically appropriate.

[q] Bone marrow biopsy is not required if PET scan is negative in marrow and if not otherwise clinically necessary by investigator discretion.

[r] Bone marrow biopsy only required to be repeated with response assessments in case of infiltration or unclear results at screening and in order to confirm a CR.

[s] Anti-pembrolizumab antibodies, pembrolizumab PK samples, thyroid function tests, chemistry, hematology/**CBC**, and urinalysis will be collected on the same day as pembrolizumab administration, which may be up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.
[t] Immunoglobulins to be collected predose at day 1.
[u] Thyroid function tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results. Thyroid function testing done at screening, the first day of pembrolizumab cycle 1 (study day 15), and then every 2 pembrolizumab cycles thereafter. Refer to Table 7-2.
[v] Done at pembrolizumab safety follow-up visit only.
[w] Hepatitis B antibodies tested at screening only; HBV viral load done at screening and at regular intervals starting at day 8 only for subjects with indeterminate HBV status (specifically for indeterminate core antibody positive, surface antibody negative, and surface antigen negative).
[x] Done on day 85 only.
[y] Monthly pregnancy testing should be conducted as per local regulations where applicable. Screening pregnancy test to be done within 72 hours prior to receiving the first dose of study medication.
[z] Blinatumomab anti-drug antibodies (serum) samples are collected at day 1 (pre-dose), D43, and safety follow-up.
[aa] Done at blinatumomab safety follow-up visit only.
[bb] Pembrolizumab anti-drug antibodies (serum) will be collected at predose (trough) within 24 hours before the following infusions of pembrolizumab: 1 (study day 15), 2 (study day 36), 4 (study day 78), 6 (study day 120), 8 (study day 162), and every 4 infusions thereafter, until 30 days after discontinuation of pembrolizumab (or until the subject starts new anticancer therapy [Table 7-2]).
[cc] Done only on the first day of pembrolizumab cycle 1 (study day 15).
[dd] Immune panel must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy.
[ee] Immune panel assessments only performed in blinatumomab cycle 1.
[ff] Blood samples for cytokine measurement will be taken in blinatumomab cycle 1 only. Cytokines must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy.
[gg] Blood samples for blinatumomab PK measurement will be taken at D1 (predose, 4, 6, 8 h after start of 9 µg/d infusion), D2 (any time), D8 (6-10 h after start of 28 µg/d infusion), D10 (any time), D15 (1 h after pembrolizumab has ended), D22 (any time), D29 (any time) and D43 (any time) in blinatumomab cycle 1 (see Section 7.3.14.1). In the expansion cohort, blinatumomab PK samples will be collected on D2 (any time), D10 (any time), D22 (any time), and D29 (any time) in cycle 1. If drug was administered via a central venous catheter, the PK sample collection should be from a peripheral site to avoid contamination of the PK samples and to better estimate PK parameters.
[hh] Blood samples for pembrolizumab PK predose samples (serum) will be collected within 24 hours before the following infusions of pembrolizumab: on the first day of pembrolizumab treatment (study day 15), cycles 2 (study day 36) , 4 (study day 78), 6 (study day 120) , and 8 (study day 162), then every 4 cycles (see Section 7.3.14.2).
[ii] **The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1). The first dose of pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events, no > grade 1 CRS and/or neurologic events.**
[jj] Pembrolizumab PK postdose samples will be collected 30 minutes post infusion on the first day of pembrolizumab treatment (study day 15), then on days 2 (study day 16), 8 (study day 22), and 15 (study day 29) of pembrolizumab cycle 1, **then 30 minutes post-infusion on** cycle 8 day 1 (study day 162), and 30 days after discontinuation of pembrolizumab (see Section 7.3.14.2).
[kk] **If available and consented to, s**ubmission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; slides or fresh frozen tissue are acceptable. Second biopsy to be collected only in subjects who consent to additional biopsies.
[ll] **If blinatumomab is interrupted per Table 6-1, the schedule of assessments will need to be repeated to align with blinatumomab dose. If re-starting at 9 µg/d repeat schedule of assessment procedures starting at D1. If re-starting at 28 µg/d repeat schedule of assessment procedures starting at D8.**

Table 7-2. Schedule of Pembrolizumab Dosing and Related Assessments For Cohort Ia (And For Part 2 if MTD is Reached in Cohort Ia)

Pembro-lizumab Cycle	Week	Study Day[a]	Pembrolizumab Dosing[a]	Anti-Pembrolizumab-Antibodies[b]	Pembrolizumab-PK Predose[c]	Pembrolizumab PK Postdose[d]	Thyroid function tests[e]	Chemistry[e]	Hematology/CBC[e]	Urinalysis[e]
Screening	-3 to - 1	-20 to 0					x	x	x	x
Cycle 1	3	15	x	x	x	x	x	x	x	x
Cycle 2	6	36	x	x	x			x	x	
Cycle 3	9	57	x				x	x	x	x
Cycle 4	12	78	x	x	x			x	x	
Cycle 5	15	99	x				x	x	x	x
Cycle 6	18	120	x	x	x			x	x	
Cycle 7	21	141	x				x	x	x	x
Cycle 8	24	162	x	x	x	x		x	x	
Cycle 9	27	183	x				x	x	x	x
Cycle 10	30	204	x					x	x	
Cycle 11	33	225	x				x	x	x	x
Cycle 12	36	246	x	x	x			x	x	
Cycle 13	39	267	x				x	x	x	x
Cycle 14	42	288	x					x	x	
Cycle 15	45	309	x				x	x	x	x
Cycle 16	48	330	x	x	x			x	x	
Cycle 17	51	351	x				x	x	x	x
Cycle 18	54	372	x					x	x	
Cycle 19	57	393	x				x	x	x	x
Cycle 20	60	414	x	x	x			x	x	
Cycle 21	63	435	x				x	x	x	x
Cycle 22	66	456	x					x	x	
Cycle 23	69	477	x				x	x	x	x
Cycle 24	72	498	x	x	x			x	x	
Cycle 25	75	519	x				x	x	x	x
Cycle 26	78	540	x					x	x	
Cycle 27	81	561	x				x	x	x	x

Footnotes defined on the next page of the table

Table 7-2. Schedule of Pembrolizumab Dosing and Related Assessments For Cohort Ia (And For Part 2 if MTD is Reached in Cohort Ia)

Pembro-lizumab Cycle	Week	Study Day[a]	Pembrolizumab Dosing[a]	Anti-Pembrolizumab-Antibodies[b]	Pembrolizumab-PK Predose[c]	Pembrolizumab PK Postdose[d]	Thyroid function tests[e]	Chemistry[e]	Hematology/CBC[e]	Urinalysis[e]
Cycle 28	84	582	x	x	x			x	x	
Cycle 29	87	603	x				x	x	x	x
Cycle 30	90	624	x					x	x	
Cycle 31	93	645	x				x	x	x	x
Cycle 32	96	666	x	x	x			x	x	
Cycle 33	99	687	x				x	x	x	x
Cycle 34	102	708	x					x	x	
Cycle 35	105	729	x				x	x	x	x
Safety FU	109	759		x		x	x	x	x	x

CBC = complete blood count; FU = follow-up; MTD = maximum tolerated dose; PK = pharmacokinetic

[a] Pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards. **The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1). The first dose of pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events, no > grade 1 CRS and/or neurologic events.**

[b] Pembrolizumab anti-drug antibodies (serum) will be collected at predose (trough) within 24 hours before the following infusions of pembrolizumab: 1 (study day 15), 2 (study day 36), 4 (study day 78), 6 (study day 120), 8 (study day 162), and every 4 infusions thereafter, and 30 days after discontinuation of pembrolizumab (or until the subject starts new anticancer therapy).

[c] Pembrolizumab PK predose samples (serum) will be collected within 24 hours before the following infusions of pembrolizumab: on the first day of pembrolizumab treatment (study day 15) and at pembrolizumab cycles 2 (study day 36), 4 (study day 78), 6 (study day 120), and 8 (study day 162), then every 4 cycles. Refer to Table 7-1.

[d] PK postdose samples will be collected 30 minutes post infusion on the first day of pembrolizumab treatment (study day 15), then on days 2 (study day 16), 8 (study day 22), and 15 (study day 29) of **pembrolizumab** cycle 1**; then 30 minutes post-infusion on** cycle 8 day 1 (study day 162), and 30 days after discontinuation of pembrolizumab. Refer to Table 7-1.

[e] Anti-pembrolizumab antibodies, pembrolizumab PK samples, thyroid function tests, chemistry, hematology/cbc, and urinalysis will be collected on the same day as pembrolizumab administration, which may be up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

Table 7-3. Schedule of Assessments for Cohort IIa and IIIa (And for Part 2 if MTD is Reached in Either of These Cohorts)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 - 57) Blinatumomab Infusion Cycle 2 (Days 85 - 113) Blinatumomab Infusion														Blinatumomab Treatment Free Period (days 58 – 84)			Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1-2 Pembrolizumab Cycle 5 [After cycle 5: Continued Pembrolizumab cycles every 21 days] (Table 7-4)														Pembrolizumab Cycle 3-4			30 days (+ 7 days) after last dose	Every 12 weeks (± 28 days)
Day (D)	D-20 to 0	D1[b,pp]	D2	D3	D8[pp]	D10	D15	**D16**	D19	D20	D26	D33	D40	D47	D54	D61	D64	D82		
Day (D)		D85	D86	D87	D92	D94	D99	**D100**	D103	D104	D110									
Protocol-Required Therapy Administration																				
Blinatumomab[c]		X	X	X	X	X	X	**X**	X	X	X	X	X	X	X					
Pembrolizumab[d]									X				X			X		X		
General Assessments																				
Informed Consent	X																			
Inclusion/Exclusion Criteria	X																			
Demographics	X																			
Medical History/Current Medical Condition	X																			
ECOG Performance Status	X																		X	
Vital signs	X	X[e]	X	X	X[e]	X	X[e]		X		X	X	X	X	X				X	
Physical Examination (including neurological examination)	X	X			X		X		X		X	X	X	X	X				X	
Height & Weight[f]	X	X																	X	
Concomitant Medication	X		Continuously throughout the study																	X[g]
AE/SAE Assessment	X[h]		Continuously throughout the study																	X[h]
Disease Related Events			Continuously throughout the study																	
Radiologic Assessments																				
Brain MRI[i]	X																			
CT scan[j,k]	X[l,m]																X[m,n]			X[m,n]
PET scan[j]	X[l]																X[n,o]			X[n,o]

Footnotes defined on the last page of the table

Table 7-3. Schedule of Assessments for Cohort IIa and IIIa (And for Part 2 if MTD is Reached in Either of These Cohorts)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 - 57) Blinatumomab Infusion Cycle 2 (Days 85 - 113) Blinatumomab Infusion														Blinatumomab Treatment Free Period (days 58 – 84)			Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 – 2 Pembrolizumab Cycle 5 [After cycle 5: Continued Pembrolizumab cycles every 21 days] (Table 7-4)														Pembrolizumab Cycle 3-4			30 days (+ 7 days) after last dose	Every 12 weeks (± 28 days)
Day (D)	D -20 to 0	D1[b,pp]	D2	D3	D8[pp]	D10	D15	**D16**	D19	D20	D26	D33	D40	D47	D54	D61	D64	D82		
Day (D)		D85	D86	D87	D92	D94	D99	**D100**	D103	D104	D110									
Local Laboratory Tests																				
Bone Marrow Biopsy[p,q]	X																X[r]			X[r]
Lumbar Puncture[p]	X																			
Chemistry[s]	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X	X	
Coagulation	X	X	X	X	X	X	X		X		X	X	X	X	X				X	
Hematology/CBC[s]	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X	X	
Immunoglobulins (IgG)		X[t]											X				X		X	
Urinalysis[s]	X								X							X			X	
Creatinine Clearance	X																			
Thyroid function tests[s,u]	X								X							X			X[v]	
HBsAg, anti-HBc, anti-HBs (screening only) and HBV viral load[w]	X	X[x]			X		X				X	X	X	X	X	X				
Pregnancy Test[y]	X																			
Central Laboratory Tests																				
Anti-Blinatumomab antibodies[z]		X											X						X[aa]	
Anti-Pembrolizumab antibodies[s,bb]									X[cc]				X					X	X[v]	
Immune panel [dd,ee]		X	X	X	X		**X**	**X**	X	**X**	X	**X**	X			**X**	X			
Serum cytokines[ff]		X[gg]	X[hh]	X[hh]	X		X[ii]	**X**	X[ii]	X			**X**							
PK Sample (Blinatumomab)[jj]		X	X		X	X	X		X		X		X							
PK Sample predose (Pembrolizumab)[s,kk]									X[cc, ll]				X					X		
PK Sample postdose (Pembrolizumab)[s,mm]									X[ll]	X[ll]	X[ll]	X[ll]							X[v]	

Footnotes defined on the last page of the table

Table 7-3. Schedule of Assessments for Cohort IIa and IIIa (And for Part 2 if MTD is Reached in Either of These Cohorts)

Blinatumomab Cycles	Screening	Treatment Period: Cycle 1 (Days 1 - 57) Blinatumomab Infusion Cycle 2 (Days 85 - 113) Blinatumomab Infusion														Blinatumomab Treatment Free Period (days 58 – 84)			Safety FU[a]	LTFU Efficacy/ Survival
Pembrolizumab Cycles	Screening	Pembrolizumab Cycles 1 – 2 Pembrolizumab Cycle 5 [After cycle 5: Continued Pembrolizumab cycles every 21 days] (Table 7-4)														Pembrolizumab Cycle 3-4			30 days (+ 7 days) after last dose	Every 12 weeks (± 28 days)
Day (D)	D-20 to 0	D1[b,pp]	D2	D3	D8[pp]	D10	D15	**D16**	D19	D20	D26	D33	D40	D47	D54	D61	D64	D82		
Day (D)		D85	D86	D87	D92	D94	D99	**D100**	D103	D104	D110									
Central Laboratory Tests (continued)																				
Core or incisional/excisional **lymph node** biopsy for biomarker analysis **(optional)[oo]**	X[nn]																X[nn]			
MRD by NGS **(plasma)[oo]**		**X**							**X**				**X**				X			

AE = adverse event; CBC = complete blood count; CNS = central nervous system; CR = complete remission; CSF = cerebrospinal fluid; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; FU = follow-up; HBc = hepatitis b core; HBs = hepatitis b surface; HBsAg = hepatitis b surface antigen; HBV = hepatitis b virus; HSCT = hematopoietic stem cell transplantation; IV = intravenous; LTFU = long-term follow-up; MRD = minimal residual disease; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NGS = next generation sequencing; PET = positron emission tomography; PK = pharmacokinetics; SAE = serious adverse event

[a] Safety follow-up will occur 30 days (+7 days) after last dose of each protocol specified therapy. If a subject starts a new anti-lymphoma treatment within 30 (± 3 days) of their last dose of protocol-assigned therapy, a safety follow-up visit should be conducted immediately prior to starting any new treatment, including HSCT conditioning regimens.

[b] All procedures completed on first day of study treatment must be completed prior to the initiation of protocol-required therapy.

[c] The initial dose of blinatumomab will be 9 µg/day and the dose will be escalated at weekly intervals until the target dose is reached. See Figure 1. **For subjects that experience a blinatumomab dose interruption during cycle 1, subjects should resume the schedule of assessments following D85-110 procedures on Table 7-3 at the start of cycle 2.**

[d] Pembrolizumab will be administered starting on study day 19 (21-day cycles). See Section 6.2.2. Pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards. For pembrolizumab dosing past cycle 5, see Table 7-4.

[e] Vital signs should be monitored continuously every 4 hours during the first 12 hours after the start of each new treatment/dose step.

[f] Height to be measured at screening only. Weight to be measured at screening, baseline, and safety follow-up visit.

[g] Recording of concomitant medication documentation during follow-up period is limited to only anti-lymphoma treatments.

[h] Report AEs occurring after enrollment only, and SAEs that occur after signing of the informed consent form. During long-term follow-up, any SAE that is determined to be related to protocol-required therapy should be reported.

[i.] Available results of brain contrast-enhanced MRI performed up to 8 weeks prior to first day of study treatment are acceptable. In case of neurologic AE ≥ grade 3 a brain MRI should be performed.
[j.] If PET scans and CT scans are done separately, they must be within the ± 3 day window and a maximum of 72 hours apart. If PET and CT are acquired on the same day, it is strongly recommended that PET is performed prior to the CT with IV contrast.
[k.] Enhanced MRI will be allowed to replace CT strictly when iodinated contrast is contraindicated.
[l.] Scans done within 28 days prior to first dose may be used in place of protocol-required assessments.
[m.] If PET scan at Screening is negative for disease involvement in the neck, screening and subsequent CT scans may not include neck. If PET scan at Screening is positive for disease involvement of the neck, subsequent CT scans must include neck.
[n.] After week 10 and during LTFU, subjects should have scans performed per the regular frequency every 12 weeks (± 3 days). PET/**CT**s should be performed until documented completeremission, progressive disease, or 24 months after the first assessment. Response assessment will also be conducted at the time of treatment discontinuation due to clinically suspected disease progression. In case of suspected pseudo-progression, repeat imaging performed 4 to 8 weeks from initial assessment suspicious for PD. Subjects who receive at least 1 full dose of pembrolizumab who discontinue from all study treatment in cycle 1, for whatever reason, shall undergo a PET/CT scan between
14 to 28 days after last pembrolizumab exposure.
[o.] For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in follow-up assessments.
[p.] Lumbar puncture and bone marrow biopsy performed up to 49 days prior to enrollment may be used in place of protocol-required assessments. An assessment of the CSF will be performed at screening if there is a concern of CNS lymphoma involvement or during treatment period if subject has a seizure. Cerebrospinal fluid, cell count, glucose, and protein will be measured at the local laboratory as part of the examination to ensure that no infiltration of the CSF by DLBCL is present. Additional investigations of the CSF should be performed as clinically appropriate.
[q.] Bone marrow biopsy is not required if PET scan is negative in marrow and if not otherwise clinically necessary by investigator discretion.
[r.] Bone marrow biopsy only required to be repeated with response assessments in case of infiltration or unclear results at screening and in order to confirm a CR.
[s.] Anti pembrolizumab antibodies, pembrolizumab PK samples, thyroid function tests, chemistry, Hematology/CBC and urinalysis will be collected on the same day as pembrolizumab administration, which may be up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.
[t.] Immunoglobulins to be collected predose at day 1.
[u.] Thyroid function tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results. Thyroid function testing done at screening, the first day of pembrolizumab cycle 1 (study day 19), and then every 2 pembrolizumab cycles thereafter. Refer to Table 7-4.
[v.] Done at pembrolizumab safety follow-up visit only.
[w.] Hepatitis B antibodies tested at screening only; HBV viral load done at screening and at regular intervals starting at day 8 only for subjects with indeterminate HBV status (specifically for indeterminate core antibody positive, surface antibody negative, and surface antigen negative).
[x.] Done at day 85 only.
[y.] Monthly pregnancy testing should be conducted as per local regulations where applicable. Screening pregnancy test to be done within 72 hours prior to receiving the first dose of study medication.
[z.] Blinatumomab anti-drug antibodies (serum) samples are collected at day 1 (pre-dose), D40, and safety follow-up.
[aa.] Done at blinatumomab safety follow-up only.
[bb.] Pembrolizumab anti-drug antibodies (serum) will be collected at predose (trough) within 24 hours before the following infusions of pembrolizumab: 1 (study day 19), 2 (study day 40), 4 (study day 82), 6 (study day 124), 8 (study day 166), and every 4 infusions thereafter, until 30 days after discontinuation of pembrolizumab (or until the subject starts new anticancer therapy) (Table 7-4).
[cc.] Done only on the first day of pembrolizumab cycle 1 (study day 19).
[dd.] Immune panel assessments only performed **during** cycle 1**, and collected on days 1, 2, 3, 8, 15, 16, 19, 20, 26, 33, 40, 61, and 64**. **Sample collection for the Immune and Cytokine panels on Days 1-16 corresponds to blinatumomab exposure, while Days 19-64 corresponds to pembrolizumab exposure.**

[ee.] Immune panel must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy.

[ff.] Cytokines must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy. **In the case of clinically relevant CRS or neurotoxicity, samples should be collected at baseline (onset of CRS or neurotoxicity), 48 hr, and 72 hrs after onset. If event not resolved by 72 hr, collect an additional sample at the time of resolution. Sample collection for the Immune and Cytokine panels on Days 1-16 corresponds to blinatumomab exposure, while Days 19-64 corresponds to pembrolizumab exposure.**

[gg.] **Blood samples for cytokine measurement will be collected for cycles 1 and 2 only. For D1, cytokine measurements will be collected on C1D1 and C2D1 (D85).**

[hh.] **Blood samples for cytokine measurements during cycle 2, but not cycle 1, will be collected on C2D2 (D86) and C2D3 (D87).**

[ii.] **Blood samples for cytokine measurements will be collected on C1D15 prior to start of blinatumomab 56 µg/d infusion in cohort IIa or 112 µg/d in cohort IIIa, and 2 and 6 hours after the start of blinatumomab infusion, and on C1D19 prior to the start of pembrolizumab infusion, and 2 and 6 hours post end of pembrolizumab infusion.**

[jj.] Blood samples for blinatumomab PK measurement will be taken at D1 (predose, 4, 6, 8 h after start of 9 µg/d infusion), D2 (any time), D8 (6-10 h after start of 28 µg/d infusion), D10 (any time), D15 (**prior to** start of 56 µg/d infusion in cohort IIa or 112 µg/d in cohort IIIa **and 2 hours and 6 hours after the start of infusion of blinatumomab**), D19 (1 h after pembrolizumab infusion has ended), D26 (any time) and D40 (any time) in blinatumomab cycle 1 (see Section 7.3.14.1). In the expansion cohort, blinatumomab PK samples will be collected on D2 (any time), D10 (any time), D22 (any time), and D29 (any time) in cycle 1. Pharmacokinetic samples must be drawn from a site that is distal to the site where the investigational product has been administered to avoid contamination of the PK samples and to better estimate PK parameters. **Sample collection for blinatumomab PK on Days 1-16 corresponds to blinatumomab exposure, while Days 19-64 corresponds to pembrolizumab exposure.**

[kk.] Blood samples for pembrolizumab PK predose samples (serum) will be collected within 24 hours before the following infusions of pembrolizumab: on the first day of pembrolizumab treatment (study day 19) and at pembrolizumab cycles 2 (study day 40), 4 (study day 82), 6 (study day 124), and 8 (study day 166), then every 4 cycles (see Section 7.3.14.2).

[ll.] **The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1). The first dose of pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events, no > grade 1 CRS and/or neurologic events.**

[mm.] Pembrolizumab PK postdose samples will be collected 30 minutes post infusion on the first day of pembrolizumab treatment (study day 19), then on days 2 (study day 20), 8 (study day 26), and 15 (study day 33) of pembrolizumab cycle 1, **then 30 minutes post-infusion on** cycle 8 day 1 (study day 166), and 30 days after discontinuation of pembrolizumab (see Section 7.3.14.2).

[nn.] **If available and consented to, s**ubmission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; slides or fresh frozen tissue are acceptable. Second biopsy to be collected only in subjects who consent to additional biopsies.

[oo.] **For MRD analysis a tumor lymph node biopsy and plasma samples will be collected if optional consent is signed. A tumor lymph node biopsy (optional) will be collected at screening, or (when available) archival tissue collected up to 3 months prior to first day of study treatment is acceptible. Plasma samples will be collected on Days 1, 19, and 40 pre-dose, and at week 10 (ie, D64), that corresponds to when a subject comes in for disease response assessment, or time of first disease response assessment if done prior to week 10 for cycles 1-2 only. Note: If no lymph node biopsy tissue is collected, then no plasma samples should be collected.**

[pp.] **If blinatumomab is interrupted per Table 6-1, the schedule of assessments will need to be repeated to align with blinatumomab dose. If re-starting at 9 µg/d repeat schedule of assessment procedures starting at D1. If re-starting at 28 µg/d repeat schedule of assessment procedures starting at D8.**

Table 7-4. Schedule of Pembrolizumab Dosing and Related Assessments For Cohorts IIa and IIIa (And For Part 2 if MTD is Reached in Either of These Cohorts)

Pembro-lizumab Cycle	Week	Study Day[a]	Pembrolizumab Dosing[a]	Anti-Pembrolizumab-Antibodies[b]	Pembrolizumab-PK Predose[c]	Pembrolizumab PK Postdose[d]	Thyroid function tests[e]	Chemistry[e]	Hematology/CBC[e]	Urinalysis[e]
Screening	-3 to- 1	-20 to 0					x	x	x	x
Cycle 1	3	19	x	x	x	x	x	x	x	x
Cycle 2	6	40	x	x	x			x	x	
Cycle 3	9	61	x				x	x	x	x
Cycle 4	12	82	x	x	x			x	x	
Cycle 5	15	103	x				x	x	x	x
Cycle 6	18	124	x	x	x			x	x	
Cycle 7	21	145	x				x	x	x	x
Cycle 8	24	166	x	x	x	x		x	x	
Cycle 9	27	187	x				x	x	x	x
Cycle 10	30	208	x					x	x	
Cycle 11	33	229	x				x	x	x	x
Cycle 12	36	250	x	x	x			x	x	
Cycle 13	39	271	x				x	x	x	x
Cycle 14	42	292	x					x	x	
Cycle 15	45	313	x				x	x	x	x
Cycle 16	48	334	x	x	x			x	x	
Cycle 17	51	355	x				x	x	x	x
Cycle 18	54	376	x					x	x	
Cycle 19	57	397	x				x	x	x	x
Cycle 20	60	418	x	x	x			x	x	
Cycle 21	63	439	x				x	x	x	x
Cycle 22	66	460	x					x	x	
Cycle 23	69	481	x				x	x	x	x
Cycle 24	72	502	x	x	x			x	x	
Cycle 25	75	523	x				x	x	x	x
Cycle 26	78	544	x					x	x	
Cycle 27	81	565	x				x	x	x	x

Footnotes defined on the next page of the table

Table 7-4. Schedule of Pembrolizumab Dosing and Related Assessments For Cohorts IIa and IIIa (And For Part 2 if MTD is Reached in Either of These Cohorts)

Pembro-lizumab Cycle	Week	Study Day[a]	Pembrolizumab Dosing[a]	Anti-Pembrolizumab-Antibodies[b]	Pembrolizumab-PK Predose[c]	Pembrolizumab PK Postdose[d]	Thyroid function tests[e]	Chemistry[e]	Hematology/CBC[e]	Urinalysis[e]
Cycle 28	84	586	x	x	x			x	x	
Cycle 29	87	607	x				x	x	x	x
Cycle 30	90	628	x					x	x	
Cycle 31	93	649	x				x	x	x	x
Cycle 32	96	670	x	x	x			x	x	
Cycle 33	99	691	x				x	x	x	x
Cycle 34	102	712	x					x	x	
Cycle 35	105	733	x				x	x	x	x
Safety FU	109	763		x		x	x	x	x	x

CBC = complete blood count; FU = follow-up; MTD = maximum tolerated dose; PK = pharmacokinetic

[a] Pembrolizumab may be administered up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards **The first dose of pembrolizumab must be delayed if blinatumomab is interrupted during the step dose period per protocol (see Table 6-1). The first dose of pembrolizumab can only be given after the blinatumomab target dose is reached (+ 4 days); also, before adding pembrolizumab, there should be no blinatumomab dose interruption due to adverse events, no > grade 1 CRS and/or neurologic events.**

[b] Pembrolizumab anti-drug antibodies (serum) will be collected at predose (trough) within 24 hours before the following infusions of pembrolizumab: 1 (study day 19), 2 (study day 40), 4 (study day 82), 6 (study day 124), 8 (study day 166), and every 4 infusions thereafter, and 30 days after discontinuation of pembrolizumab (or until the subject starts new anticancer therapy).

[c] Pembrolizumab PK predose samples (serum) will be collected within 24 hours before the following infusions of pembrolizumab: on the first day of pembrolizumab treatment (study day 19) and at pembrolizumab cycles 2 (study day 40), 4 (study day 82), 6 (study day 124), and 8 (study day 166), then every 4 cycles. Refer to Table 7-3.

[d] PK postdose samples will be collected 30 minutes post infusion on the first day of pembrolizumab treatment (study day 19), then on days 2 (study day 20), 8 (study day 26), and 15 (study day 33) of **pembrolizumab** cycle 1**: then 30 minutes post-infusion on** cycle 8 day 1 (study day 166), and 30 days after discontinuation of pembrolizumab. Refer to Table 7-3.

[e] Anti pembrolizumab antibodies, pembrolizumab PK samples, thyroid function tests, chemistry, Hematology/CBC and urinalysis will be collected on the same day as pembrolizumab administration, which may be up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

Refer to the applicable supplemental laboratory, imaging, and home healthcare manuals for detailed collection and handling procedures.

7.2 General Study Procedures

7.2.1 Screening and Enrollment

Screening procedures are to be completed during the screening time period at the times designated in the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4).

All subjects or their legally acceptable representative (ie, legal guardian) must sign and date the most current IRB/IEC approved ICF. Confirmation that the ICF has been signed should occur before any study specific procedures are performed.

All subjects who are enrolled and receive protocol-specified therapy should be re-consented with any updated versions of IRB/IEC approved informed consents during study participation applicable and per institutional guidelines.

7.2.2 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4). Administration of protocol-required therapies is to be administered last during each visit that it is required.

- Physical Examination
- PK (including intensive PK assessments)
- Vital signs (eg, blood pressure, heart rate, respiration rate, temperature)
- Laboratory Assessments including local and central laboratories, as applicable
- Imaging Assessments
- Serious Adverse Event reporting
- Adverse Event reporting
- Disease Related Event Reporting
- Documentation of concomitant medications
- Receipt of protocol-required therapies

If a subject stops treatment (eg, due to an adverse event), the investigator must ensure there is a plan for continued follow-up until the subject completes all protocol-required visits or withdraws from the study.

7.2.3 Safety Follow-up Visit

All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of each study treatment. Serious adverse events (and any concomitant medications associated with serious adverse events) observed by the investigators or reported by the subjects that occur within 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy (whichever is earlier) will be reported, followed, and recorded.

For all subjects, 2 safety follow-up visits should be performed: 30 days (+ 7 days) after the last dose of blinatumomab and 30 days (+ 7 days) after the last dose of pembrolizumab.

If a subject starts a new anti-lymphoma treatment within 30 (± 3) days of their last dose of protocol-assigned therapy, a safety follow-up visit should be conducted immediately prior to starting any new treatment, including HSCT conditioning regimens.

7.2.4 Long-term Follow-up

After the safety follow-up visit, all subjects will enter long-term follow-up. Subjects who end blinatumomab treatment but continue pembrolizumab monotherapy will be considered to be in long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) following blinatumomab safety follow-up visit until approximately 24 months from the last dose of pembrolizumab. In case that a subject continues pembrolizumab monotherapy (and until monotherapy ends), this long-term follow-up schedule will occur in parallel with the schedule of assessments of pembrolizumab dosing and related assessments. In addition, treatment related adverse events that occur through the end of the long-term follow-up period will be reported.

7.2.5 End of Study

The end of study for each subject is defined as the date the subject withdraws full consent from the study, completes the final safety follow-up visit or final long-term follow-up visit (whichever is later) or death.

7.3 Description of Study Procedures

An overview of study assessments/procedures is provided below. Refer to the eCRF completion guidelines for data collection requirements and documentation of study assessments/procedures.

7.3.1 Informed Consent

All subjects or their legally acceptable representative (ie, legal guardian) must sign and date the most current IRB/IEC approved ICF. Confirmation that the ICF has been signed should occur before any study specific procedures are performed.

All subjects who are enrolled and/or receive protocol-specified therapy should be re-consented with any updated versions of IRB/EC approved informed consents during study participation as applicable and per institutional guidelines.

In countries where foreign subjects can be enrolled according to local regulations (agreement by responsible IRB/IEC required), specific requirements for the process of consenting subjects as well as for the conduct of the study visits will apply. It is the investigator´s responsibility to ensure that the subject will understand the ICF and that the subject will be able to communicate appropriately with the investigator, study team, and ambulant care service provider, if applicable (eg, by translation of the ICF into the subject`s native language and providing an interpreter, as applicable). The investigator should also highlight the importance of attending applicable follow-up visits and collection of Long-Term Follow-up data (eg, overall survival (OS), additional anticancer therapy) to all subjects during the informed consent process.

7.3.2 Demographics

Demographic data that will be collected include sex, date of birth, and ethnicity to study their possible association with subject safety and treatment effectiveness.

7.3.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started 5 years prior to screening through the time of enrollment. Medical history will include information on the subject's concurrent medical conditions. Diffuse large B-cell lymphoma history must date back to the initial diagnosis.

In addition to the medical history noted above, all history related to the subject's diagnosis of DLBCL (eg, date of initial diagnosis, additional risk factors at diagnosis, cell-of-origin [COO] at any timepoint if available [immunohistochemistry pattern, GEP/other], BCL-2 fluorescence in situ hybridization (FISH): translocation, immunohistochemistry expression levels], c-myc [FISH: translocation, immunohistochemistry expression levels]) will be recorded.

7.3.4 ECOG Performance Status

Assessment of the subject's performance status will be performed at screening and 30 days after each treatment end using the ECOG score (see Appendix D).

7.3.5 Physical Examination

Physical examinations will be completed as per standard of care. All clinically relevant findings will be documented. Physical examination will also include a neurological exam. Body height (only at screening) and weight will also be documented. Body temperature (eg, oral or tympanic), supine heart rate, and blood pressure (systolic/diastolic) will be measured at regular intervals during the study. The investigator should monitor the subject's vital signs continuously every 4 hours during the first 12 hours after the start of each new blinatumomab treatment/dose step. Vital sign measurements will be repeated daily during the subject's hospitalization.

7.3.6 Neurological Examinations

Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, and neuropsychological findings, (eg speech, cognition, and emotion). A neurological exam should also be performed in the case of grade 3 or higher neurologic events.

7.3.7 Hepatitis B Antigen, Anti-Hepatitis B core Antigen, and Anti-Hepatitis B Surface Antigen

Hepatitis b surface (HBs) antigen, HBs antibody, and hepatitis b core (HBc) antibody will be tested at screening for all subjects. For subjects with history of seronegative HBV exposure or indeterminate HBV status (anti-Hbc antibody positive, anti-HBs antibody negative, and anti-HBs antigen negative), HBV DNA viral load should be performed at screening and at regular intervals during blinatumomab treatment to monitor for HBV re-activation.

7.3.8 Lumbar Puncture and CSF Assessment

An assessment of the cerebrospinal fluid (CSF) will be performed at screening if there is a concern of CNS lymphoma involvement or during treatment period if subject has a seizure. Cerebrospinal fluid, cell count, glucose, and protein will be measured at the local laboratory as part of the examination to ensure that no infiltration of the CSF by DLBCL is present. Lumbar puncture performed up to 49 days prior to enrollment may be used in place of protocol-required assessments. Additional investigations of the CSF

should be performed as clinically appropriate. Cerebrospinal fluid analysis will occur each time lumbar puncture is performed.

7.3.9 Brain MRI or CT

A brain MRI is required for all subjects at screening**; if MRI is contraindicated (eg, pacemaker, implant, et al) a CT can be performed**. Available results of brain contrast-enhanced MRI **or CT** performed up to 8 weeks prior to first day of study treatment are acceptable. In case of neurological adverse event of grade 3 or higher, a brain MRI **or CT** should be performed.

7.3.10 Bone Marrow Biopsy

A bone marrow biopsy will be performed at screening. Bone marrow biopsy is only required to be repeated with response assessments in case of infiltration or unclear results at screening and in order to confirm a CR. Available results of routine samples will be taken up to 49 days prior to enrollment. Bone marrow biopsy is not required if positron emission tomography (PET) scan is negative in marrow and if not otherwise clinically necessary by investigator discretion.

7.3.11 Core or Incisional/Excisional Biopsy for Biomarker Analysis, MRD by NGS, Cell of Origin, and FISH Analysis (optional)

If as part of the standard institutional procedure, and subject signs the optional consent, a tumor affected lymph node **or** tissue sample **for the diagnosis of relapsed/refractory DLBCL will be collected for subjects enrolled into the study**. **In addition, a second biopsy is to be collected only in subjects who consent to additional biopsies. Samples should be collected 10 weeks after starting blinatumomab.** Sites will process all tissue samples as outlined in the laboratory manual. Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; slides or fresh frozen tissue are acceptable. All tissue sample preparation guidelines and requirements will be outlined in the laboratory manual.

Tissue will be used for exploratory analyses which may include and not be limited to MRD and immunohistochemistry (IHC). In addition, cell of origin analysis may be performed to determine DLBCL subtypes, and FISH analysis may be performed to determine gene rearrangements associated with double/triple hit DLBCL, if this information is not reported in the CRF under Medical History (see Section 7.3.3).

7.3.12 Tumor Response Assessment

7.3.12.1 Assessment of Disease and Tumor Imaging

PET/CT scans with whole body images, from base of skull to mid-thigh, will be conducted. If PET scan at screening is negative for disease involvement in the neck, screening and subsequent CT scans may not include neck. **PET/CT** should be performed until **documented complete remission, PD, or** 24 months after the first assessment**.** Imaging is not required beyond confirmed progression (unless subject meets criteria to continue therapy beyond radiographic progression as outlined in Section 7.3.12.4). For lymphomas that are not fluorodeoxyglucose (FDG)-avid at screening, PET does not need to be repeated in follow-up assessments.

Examinations should be consistent across timepoints and include the following information: amount of tracer, location of injection, arm location, scan delay. The following data should be collected per site: standard procedures, height, weight, gender, administration dose, time between dose administration and imaging, blood glucose level, time between blood glucose level sampling, and tracer injection.

PET images should be converted to standardized uptake value maps to support comparison across timepoints and to standardize viewing conditions; CT and anatomical coverage includes neck, chest, abdomen, and pelvis.

Enhanced MRI will be allowed to replace CT strictly when iodinated contrast is contraindicated.

Criteria for Assessment of Disease

Antitumor activity will be evaluated using the following criteria:

- **Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification** (Cheson et al, 20**14***)* (Appendix I)
- Revised Response Criteria for Malignant Lymphoma. (Cheson et al, 2007*)* **(Appendix J)**

  The **Lugano Classification (Cheson et al, 2014)** will be applied by the site as the primary measure for **subject eligibility,** assessment of disease response and as a basis for all protocol guidelines related to disease status **and subject management** (eg, discontinuation of study therapy). **Meanwhile, Cheson 2007 Revised Response Criteria will continue to be used for the assessment of disease response to keep consistency through the study.**

7.3.12.2 Initial Disease Assessment

Initial disease assessment or tumor imaging must be performed within 28 days prior to the first dose of trial treatment. The site study team must review pre-trial images to confirm the subject has measurable disease as defined in the inclusion criteria.

Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. Computed tomography and PET should be used throughout the study at time-points designated in Schedule of Assessments (Table 7-1 and Table 7-3). For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in follow-up assessments.

7.3.12.3 Timing of Disease Assessments

Uniform disease response assessments will occur initially at 10 weeks **(D64)** (± 3 days) after treatment start of blinatumomab and thereafter every 12 weeks (± 3 days). **PET/CT** should be performed until documented complete remission, PD, or 24 months after the first assessment. Response assessment will also be conducted at the time of treatment discontinuation due to clinically suspected disease progression. If PET scans and CT scans are done separately, they both must be within the ± 3-day window and a maximum of 72 hours apart. If PET and CT are acquired on the same day, it is strongly recommended that PET is performed prior to the CT with IV contrast. Subjects who receive at least 1 full dose of pembrolizumab who discontinue from all study treatment in cycle 1, for whatever reason, shall undergo a PET/CT scan between 14 to 28 days after last pembrolizumab exposure.

7.3.12.4 Disease Assessments During the Trial

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as pembrolizumab.

In the setting where a subject's assessment shows unconfirmed PD by investigator assessment, study drug may be continued upon sponsor consultation if the investigator considers the subject is clinically stable, and repeat imaging performed in 4-8 weeks from initial assessment suspicious for PD. Subjects that remain on treatment after the

first suspicion of progression who then become clinically unstable are not required to have repeat imaging for confirmation.

Clinical Stability may be defined as:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Imaging should also occur at any time when there is clinical suspicion of progression. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued/resumed. If repeat imaging confirms PD by investigator assessments, subjects will be discontinued from study therapy.

7.3.13 Laboratory Assessments

The analyses for all laboratory tests used throughout this study are listed in Table 7-5. Bone marrow biopsy, lumbar puncture, chemistry, thyroid function tests, coagulation, hematology, IgG, urinalysis, creatinine clearance (CrCl), and pregnancy tests will be performed locally. Anti-blinatumomab and anti-pembrolizumab antibodies, immune panel, serum cytokines, PK samples, core or incisional/excisional biopsy, and MRD by NGS will be evaluated centrally. Anti-pembrolizumab antibodies, pembrolizumab PK samples, thyroid function tests, chemistry, hematology/complete blood count (CBC), and urinalysis will be collected on the same day as pembrolizumab administration, which may be up to 3 days before or after each scheduled day 1 from pembrolizumab cycle 2 onwards.

Amgen or the central laboratories will supply containers for sample collection, preparation, packaging and shipping. Detailed instructions for sample collection, processing, and shipping are provided in the central laboratory manual and/or Amgen-provided training materials. The date and time of sample collection will recorded in the source documents at the site.

Blood draws should not be done via the central venous access. Exception: If a permanent central line with more than 1 lumen is used, blood draws can be done via the lumen that is not used for drug administration. Pharmacokinetic sample collection must be from the opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, the PK sample collection should be from a peripheral site.

Table 7-5. Laboratory Assessments

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium Potassium Chloride Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Uric acid Alkaline phosphatase LDH AST (SGOT) ALT (SGPT) C-reactive protein Amylase Lipase Bilirubin (total) GGT	INR Fibrinogen aPTT Thyroid Function TSH T3 or Free T3 Free T4	Blood Protein Glucose	Hemoglobin Hematocrit Reticulocytes Platelets WBC RBC Differential •Neutrophils •Bands/stabs •Eosinophils •Basophils •Lymphocytes •Monocytes	Bone marrow Lumbar Puncture[a] Anti-blinatumomab Antibodies Anti-Pembrolizumab Antibodies IgG PK (blinatumomab and pembrolizumab) CSF analytes Biomarkers Pregnancy test Serum Cytokines Immune panel MRD by NGS HBs HBc

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; GGT = gamma-glutamyl transferase; IgG = immunoglobulin G; HBc = hepatitis B core; HB**s** = hepatitis b surface; INR = international normalized ratio; LDH = lactate dehydrogenase; MRD = minimal residual disease; NGS = next generation sequencing; PK = pharmacokinetic;; RBC = red blood cells; SGOT = serum glutamic oxaloacetate transaminase; SGPT = serum glutamate pyruvate transaminase; TSH = thyroid stimulating hormone; WBC = white blood cells.
[a] Lumbar puncture only required if concerns of disease presence per investigator judgement

7.3.14 Pharmacokinetic Assessments

7.3.14.1 Blinatumomab

Pharmacokinetic (PK) assessments will be required for all subjects receiving blinatumomab.

In cohort Ia, blinatumomab samples will be collected at day 1 (predose, 4, 6, 8 h after start of 9 µg/d infusion), day 2 (any time), day 8 (6 - 10 h after start of 28 µg/d infusion), day 10 (any time), day 15 (1 hour after pembrolizumab infusion has ended in cohort Ia), day 22 (any time), day 29 (any time) and day 43 (any time) in cycle 1. In cohorts IIa and IIIa, blinatumomab samples will be collected on day 1 (predose, 4, 6, 8 hours after start of 9 µg/d infusion), day 2 (any time), day 8 (6 -10 hours after start of 28 µg/d infusion), day 10 (any time), day 15 (**prior to** start of 56 µg/d infusion in cohort IIa or 112 µg/d infusion in cohort IIIa **and 2 hours and 6 hours after the start of infusion of blinatumomab**), day 19 (1 hour after pembrolizumab infusion has ended), day 26 (any time), and day 40 (any time) in cycle 1.

In the expansion cohort, blinatumomab PK samples will be collected on day 2 (any time), day 10 (any time), day 22 (any time), and day 29 (any time) in cycle 1.

7.3.14.2 Pembrolizumab

Pharmacokinetic assessments will be required for all subjects receiving pembrolizumab.

For cohort Ia, PK samples will be collected at predose (within 24 hours before infusion) before the following infusions: on first day of pembrolizumab treatment (study day 15) and at pembrolizumab cycles 2 (study day 36), 4 (study day 78), 6 (study day 120), and 8 (study day 162), then every 4 cycles. Pharmacokinetic postdose samples will be collected 30 minutes post infusion on the first day of pembrolizumab treatment (study day 15), then on days 2 (study day 16), 8 (study day 22), and 15 (study day 29) of pembrolizumab cycle 1, cycle 8 day 1 (study day 162), and 30 days after discontinuation of pembrolizumab.

For cohorts IIa and IIIa, PK samples will be collected at predose (within 24 hours before infusion) before the following infusions: on the first day of pembrolizumab treatment (study day 19), and at pembrolizumab cycles 2 (study day 40), 4 (study day 82), 6 (study day 124), and 8 (study day 166); then every 4 cycles.

For cohorts IIa and IIIa, pembrolizumab PK postdose samples will be collected 30 minutes post infusion on the first day of pembrolizumab treatment (study day 19), then on days 2 (study day 20), 8 (study day 26), and 15 (study day 33) of

pembrolizumab cycle 1, cycle 8 day 1 (study day 166), and 30 days after discontinuation of pembrolizumab.

The pembrolizumab PK samples should be completed during the study visits as defined by the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4).

7.3.15 Immunoglobulins

Immunoglobulins (IgG only) will be collected at time points outlined in the Schedule of Assessments (Table 7-1, and Table 7-3) to detect hypogammaglobulinemia or immunological changes.

7.4 Antibody Testing Procedures

Blood sample(s) will be collected at time points as outlined in the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4) for the measurement of anti-blinatumomab and anti-pembrolizumab binding antibodies.

Samples testing positive for binding antibodies may be further characterized for quantity/titer, isotype, affinity, in vitro neutralizing activity, and presence of immune complexes. Additional blood samples may be obtained to rule out anti-drug antibodies during the study.

Subjects who test positive for binding antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab or anti-pembrolizumab antibody response may also be asked to return for additional follow-up testing.

7.5 Biomarker Development

7.5.1 Immune Panel by Flow Cytometry

For subjects on blinatumomab, this assay will be used to monitor changes in lymphocytes (B-cell and T-cell populations) and leukocyte populations (leukocytes, lymphocytes, monocytes, and granulocytes) in peripheral blood. The rationale for an aggressive sample collection in the treatment period is to better understand the mechanism of action of the T cell response **with the addition of pembrolizumab to blinatumomab,** as well as potential drug resistance mechanisms.

The collection schedule is extensive to ensure adequate data is collected to better understand the mechanism of action of the T cell response elicited by the dual agent therapy, association with clinical response, and adverse events. In cohort Ia, samples will be collected days 1, 2, 3, 8, 10, 22, 43 and 64. In cohorts IIa and IIIa, samples will be collected days 1, 2, 3, 8, **15**, **16,** 19, **20,** 26, **33,** 40, **61,** and 64. All samples will be collected in the first (induction) cycle of blinatumomab only. Immune panel samples

must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy.

7.5.2 Serum Cytokines

To monitor activation of immune effector cells, blood samples for measurement of peripheral blood cytokine levels will be taken as per the Schedule of Assessments. In cohort Ia, blood samples will be collected **on** days 1, 2, 3, 8, 15, and 22 based on the previous phase 2 blinatumomab experience. In cohorts IIa and IIIa, blood samples will be collected **on** days 1, **2, 3,** 8, 15, **16,** 19, 20**, and 40 during cycle 1 to further understand how the addition of pembrolizumab affects cytokine levels in combination with blinatumomab. For cycle 2, samples will be collected on days 85, 86, and 87 to understand how pembolizumab effects cytokine levels when blinatumombab treatment resumes after the blinatumomab treatment-free interval**. Cytokine samples must be drawn after dexamethasone premedication but no more than 15 minutes before initiation of blinatumomab therapy. Blood samples for cytokine measurement are also to be collected in cases of grade ≥3 neurological events or CRS.

7.5.3 MRD by NGS (Next Generation Sequencing)

The presence or absence of MRD is becoming an increasingly important factor in hematologic malignancies and has been a key measure of the depth and quality of the treatment response in other blinatumomab studies. While **using circulating tumor DNA (ctDNA) from plasma to measure** MRD in DLBCL is a relatively nascent field, studies have suggested inferior outcomes in subjects who have detectable MRD compared to those without detectable disease following treatment (Roschewski et al, 2015). **Plasma ctDNA will be used to measure MRD using NGS to analyze gene rearrangements of the B-Cell receptor repertoire. Multiple time points will be analyzed to determine if MRD can be used to monitor early response or progression before disease assessments are obtained. If optional consent is signed, tumor tissue at screening and plasma samples on days 1, 19, 40, and week 10 (ie, day 64), or time of first disease response assessment (if done prior to week 10), will be collected for MRD assessment for cycles 1 and 2. If no lymph node biopsy tissue is collected at screening, then no plasma samples should be collected.**

7.6 Sample Storage and Destruction

Any blood, biomarker, PK, or tumor sample collected according to the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject or legally acceptable representative, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand DLBCL, the dose response and/or prediction of response to blinatumomab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetics or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood, biomarker, PK, or tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigating physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 7-1, Table 7-2, Table 7-3, and Table 7-4) and collection of data, including endpoints, adverse events, disease related events, and device related events, as applicable. The investigator must document the change to the Schedule of Assessments and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Subject or legally acceptable representative request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- confirmed disease progression

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

8.4 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- **The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.**
- **In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.**
- **If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.**
- **For subjects who are lost to follow-up, the investigator can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.**

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease (Table 9-1). Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition. All serious Disease Related Events will be recorded and reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event.

Disease Related Events that do not qualify as Adverse Events or Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.
- Death due to the disease under study is to be recorded on the Event CRF

Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition

  OR

- If the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening

  AND

- The event must meet at least 1 of the serious criteria

Table 9-1 outlines the expected disease related adverse events by system organ class.

Table 9-1. Disease Related Adverse Events by System Organ Class

SOC	Preferred Terms
Blood and lymphatic system disorders	lymphadenopathy
General disorders and administration site conditions	disease progression fatigue
Investigations	weight decreased
Skin and subcutaneous tissue disorders	night sweats

SOC = system organ class

9.1.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's

legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease Related Event as defined in Section 9.1.1):

- fatal
- life threatening (places the subject at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A disease related event (eg, disease progression) is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria.

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention. Serious adverse events, or follow-up to a serious adverse event, must be reported within 24 hours for the time period beginning with signing of informed consent through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

9.1.4 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as ECI and must be reported to the sponsor.

For the time period beginning when the consent form is signed until start of treatment, any ECI, or follow-up to an ECI, that occurs to any subject must be reported within 24 hours to the sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at start of treatment through 30 days following cessation of treatment, any ECI, or follow-up to an ECI, whether or not related to the sponsor's product, must be reported within 24 hours to the sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- an overdose of sponsor's product, as defined in Section 6.2.1.1 and Section 6.2.1.1 - Definition of an overdose for this protocol and reporting of overdose to the sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT lab value that is greater than or equal to 3x the upper limit of normal (ULN) and an elevated TBL lab value that is greater than or equal to 2x the ULN and, at the same time, an ALP lab value that is less than 2x the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

  Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through the last safety follow-up visit that occurs 30 days (+ 7 days) following the last dose of study medication are recorded on the Event CRF as a Disease Related Event.

All serious disease related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease related event data to the sponsor within 24 hours of it being available.

Disease Related Events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events and recorded and reported per Section 9.2.2.2 and Section 9.2.2.3.

Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF as a serious Disease Related Event and should be recorded and reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event.

9.2.2 Adverse Events

9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the last safety follow-up visit that occurs 30 days (+7 days) following the last dose of study medication are reported using the event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s) if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity (and/or toxicity)
- Assessment of relatedness to protocol-required therapies
- Action taken

If the severity of an adverse event changes from the date of onset to the date of resolution, it should be captured as a new event for each grade change on the Event eCRF.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug-related by the investigator.

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the investigational products. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational products?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, device[s] and/or procedure [including any screening procedure(s)]. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, device(s)), and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. All grade 3 and grade 4 laboratory values should be recorded as adverse events. In addition, if signs or symptoms are associated with a laboratory abnormality, the signs/symptoms and the laboratory abnormality should all be recorded as adverse events. The laboratory abnormality and any signs/symptoms should be graded according to their own CTCAE criteria.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are recorded in the subject's medical record and are submitted to Amgen. During long-term follow-up, any serious adverse event that is determined to be related to protocol-required therapy should be reported. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the EDC system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event.

See Appendix B for a sample of the Serious Adverse Event Worksheet /eSAE Contingency Report Form.

The investigator must assess whether the serious adverse event is possibly related to the investigational product(s). This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational products. Investigational products in this study are blinatumomab and pembrolizumab.

The investigator is expected to follow reported serious adverse events until stabilization or resolution.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will comply with all international and national regulations on Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to Regulatory Agencies.

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, EU member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking blinatumomab or pembrolizumab, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur within 120 days after the last dose of protocol-required therapies.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur within 120 days after the last dose of protocol-required therapies.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints and Analysis Sets

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- Incidence of DLTs

10.1.1.2 Secondary Endpoints

- Objective response (including CR and PR) by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab and during the treatment period**
- Complete response by **the Lugano Classification (Cheson et al, 2014) and Revised Response Criteria (Cheson et al, 2007) during the first 12 weeks since starting blinatumomab and during the treatment period**
- Progression free survival: will be calculated as the time from the date of first dose of blinatumomab until the date of diagnosis of progression of lymphoma, or date of death, whichever is earliest. **For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET/CT using Lugano Classification will be used.** Subjects who are alive and did not have progression will be censored at the last **radiological non-missing evaluable** tumor assessment **date**. Progression free survival for subjects who were enrolled in dose cohorts that were not selected for the extension cohort will not be calculated.
- Overall survival: will be calculated as the time from the date of first dose of blinatumomab until death due to any cause. Subjects who are alive at the date that triggers the analysis will be censored at the date last known to be alive.
- Duration of response: calculated only for subjects who achieve an OR **(ie,** CR or PR**) during the first 12 weeks since starting blinatumomab**. The duration will be calculated from the date a response, CR or PR, is first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurs first. **For diagnosis of progression of lymphoma, the progression of radiographic assessment of PET/CT using Lugano Classification will be used.** Subjects who do not have a relapse event will be censored on their last **radiological non-missing evaluable tumor assessment date**. A sensitivity analysis will censor subjects who receive an autologous HSCT/allogenic HSCT at the time of autologous HSCT/allogenic HSCT unless there is no assessment after the autologous HSCT/allogenic HSCT, in which case the last assessment prior to the autologous HSCT/allogenic HSCT will be used as the censoring time.
- Blinatumomab PK parameters
- Pembrolizumab PK parameters

Note that “remission” in this context equates to “response”.

10.1.1.3 Safety Endpoints

- Incidence and severity of adverse events

10.1.1.4 Exploratory Endpoints

- Tumor PD-L1 expression will be assessed pre-treatment and on treatment to explore potential correlation with clinical outcomes
- Changes in Lymphocytes (B-cell, T-cell populations, NK cells) and leukocyte populations (leukocytes, lymphocytes, monocytes, and granulocytes) in peripheral blood
- Peripheral blood cytokine levels
- Minimal residual disease (MRD) by NGS after cycle 1 of blinatumomab

10.1.2 Analysis Sets

10.1.2.1 DLT Evaluable Analysis Set

Dose limiting toxicity evaluable analysis sets include all subjects who are DLT evaluable. To be DLT evaluable, subjects must meet one of the following criteria during DLT evaluation period:

- The subject experienced a DLT; OR
- The subject was removed from treatment for an adverse event/toxicity that is not a DLT, if the subject has been exposed to both investigational products **for at least 12 days since pembrolizumab initiation with blinatumomab at the target dose**; OR
- The subject was removed from treatment for reasons other than an adverse event/toxicity (ie, disease progression), and the subject has been exposed to both investigational products for at least 12 days since pembrolizumab initiation with blinatumomab at the target dose; OR
- The subject did not experience a DLT and completed the DLT evaluation period

10.1.2.2 Full Analysis Set

The full analysis set includes all subjects who received blinatumomab.

10.1.2.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set includes all subjects who received any infusion of blinatumomab and pembrolizumab and have at least 1 pharmacokinetic sample collected.

10.1.2.4 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set includes all subjects who receive any infusion of blinatumomab and have at least 1 pharmacodynamic sample collected.

10.1.3 Subgroups

- Sex (male vs female)
- Race/ethnicity (categories depend on the data, all races with less than 5% of the total enrolled subjects will be pooled together for summary purposes)
- Age group (< 65 vs ≥ 65 and < 75 vs ≥ 75 years old)
- Region (North America, Europe, and rest of the world [ROW]). If any region has small number of subjects, it will be combined with other regions)

- Additional subgroups may be explored, including but not limited to:
  - Number of prior salvage therapies (0 vs 1 vs ≥ 2)
  - B:T cell ratio at baseline
  - PD-L1 positivity

10.1.4 Handling of Missing and Incomplete Data

Subjects without tumor response assessments will be considered as non-responders. Otherwise, only non-missing data will be analyzed. No other missing value replacement procedure will be deployed for clinical data.

10.2 Sample Size Considerations

Part 1

A rolling 6 dose design will be used. An additional 4 subjects per cohort can be enrolled to further evaluate safety and PK data if needed. There will be a minimum of 6 subjects and a maximum of 30 subjects enrolled.

Part 2

Forty subjects will be enrolled in Part 2. With 40 subjects, the 95% exact confidence interval (Clopper and Pearson, 1934) for the estimate of ORR can be calculated. The 95% confidence intervals for some ORRs are shown in the table below.

Table 10-1. Estimated 95% Confidence Interval for ORR

ORR	95% Confidence Interval
0.40	(0.25, 0.57)
0.45	(0.29, 0.61)
0.50	(0.34, 0.71)
0.55	(0.38, 0.71)
0.60	(0.43, 0.75)

ORR = objective response rate

10.3 Planned Analyses

10.3.1 Interim Analyses

DRT will conduct evaluations of efficacy for ORR by the Lugano Classification (Cheson et al, 2014) during the first 12 weeks since starting blinatumomab and safety for DLT rate to assess if the threshold for early trial termination has been reached.

Table 10-2 shows the efficacy stopping rules using a Bayesian approach to potentially terminate the study if the posterior probability that ORR is less than 50% is > 80%. The stopping boundaries assume a prior beta distribution (1, 1). The operating characteristics in Table 10-3 provide the probability of stopping the trial early for given hypothetical true ORR.

Table 10-2. Efficacy stopping Boundary With Batch Size of 10 Subjects, Posterior Probability of 80% and ORR of 50%

Number of DLT evaluable subjects	Stop study if observing these many DLTs
10	≤ 3
20	≤ 8
30	≤ 12
40	Always stop

Table 10-3. Operating Characteristics With Batch Size of 10 Subjects

True ORR	Prob of Stopping Early	Average Sample Size
0.40	70%	23
0.45	52%	27
0.50	34%	32
0.55	19%	19
0.60	9%	38

Table 10-4 shows the **safety** stopping rules us**ing** a Bayesian approach to terminate the study if the posterior probability that the DLT rate is greater than 25% is > 90%. The stopping boundaries assume a prior beta distribution (0.50, 1.50). The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 10-5 provide the probability of stopping the trial early for given hypothetical true DLT rates.

Table 10-4. Safety Stopping Boundary With Batch Size of 10 Subjects, Posterior Probability of 90% and DLT Limit of 25%

Number of DLT evaluable subjects	Stop study if observing these many DLTs
10	**≥ 5**
20	**≥ 8**
30	**≥ 11**
40	**Always stop**

DLT = dose limiting toxicity

Table 10-5. Operating Characteristics With Batch Size of 10 Subjects

True DLT Rate	Prob of Stopping Early	Average Sample Size
0.20	**6**%	**38**
0.25	**17**%	**36**
0.30	**36**%	**32**
0.35	**57**%	27
0.40	**76**%	22

DLT = dose limiting toxicity; prob = probability

10.3.2 Dose Level Review Team and Data Review Team (DRT)

10.3.2.1 Dose Level Review Team

A DLRT will review safety data from each cohort in part 1 to recommend if blinatumomab and pembrolizumab in combination is safe and tolerable as defined by DLT criteria and general clinical judgement, taking into account a general benefit risk assessment. Pharmacokinetic data may be reviewed, if available. Based on the totality of the data, the DLRT may recommend to declare MTD, to escalate to the next dose level, to expand a cohort to a maximum of 10 subjects if the collection of more data is deemed warranted, or to adjudicate the DLT criteria. The DLRT will meet to confirm the decision rules when any of the following criteria are met:

- In 2 or more out of 6 or 3 or more out of 10 subjects, a DLT has been reported in a cohort
- 6 subjects are enrolled in a cohort and all subjects have completed the DLT observation period
- In the event that a cohort is expanded to 10, DLRT will also meet after all subjects have completed DLT observation period

The DLRT will consist of, at minimum, members from the Amgen study team, including at least one clinician, one safety representative, members outside the Amgen study team including, at least one representative of the Merck study team, and one investigator participating in the study who has recruited subjects into the cohort under

review. A cohort may be expanded by DLRT recommendation in the case that the data suggests a change to the anticipated risk/benefit profile, warranting collection of further data at the blinatumomab target dose.

In part 2, **DRT** will meet after every **10** subjects become DLT evaluable.

10.3.2.2 Data Review Team

A DRT is a group, internal to Amgen but external to the product team, that reviews accumulating data from the ongoing clinical trial to evaluate overall benefit and risk. The DRT includes a clinician, a safety physician, and a biostatistician. Experts external to Amgen may be included if needed. Membership, procedures and meeting timing will be described in detail in the study DRT charter.

10.3.3 Primary Analysis

The primary analysis will occur after the last subject in part 2 has had an opportunity to complete **response** assessment **during** 12 weeks **since** starting blinatumomab.

10.3.4 Final Analysis

The final analysis will occur when the last subject has had the opportunity to complete the long-term follow-up period, which is following blinatumomab safety follow-up visit until approximately 24 months from the last dose of pembrolizumab.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

The analyses will be performed by cohorts for part 1. The analyses for part 2 will combine subjects in part 2 and the cohort in part 1 with selected dose for part 2 unless specified otherwise. Continuous variables will be summarized by the nonmissing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Time to event endpoints will be summarized with hazard ratios, Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 9**5**% confidence intervals including estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934). Pharmacokinetics will be performed by noncompartmental analysis. Pharmacodynamic samples will be summarized by

descriptive statistics. Relationships among drug exposures and efficacy, safety, and biomarkers may be explored if the data are sufficient.

10.4.2 Methods of Analysis

The analyses will be performed on the Full Analysis Set unless specified otherwise.

10.4.2.1 Primary Endpoint

The incidence of DLTs will be summarized. The DLT rate is based on the number of subjects in the DLT analysis set.

10.4.2.2 Secondary Efficacy Endpoints

The percentage of subjects with an objective response **using the Lugano Classification and Revised Response Criteria during** 12 weeks **since** starting blinatumomab will be summarized with an exact 2-sided binomial 9**5**% confidence interval, respectively. **The percentage of subjects with an objective response using the Lugano Classification during the entire treatment period will also be summarized.** Subjects missing post baseline disease assessments will be considered not to have achieved an objective response.

The KM summaries will be performed for PFS, OS, and **DOR**.

10.4.2.3 Secondary Safety Endpoints

Adverse Events:

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events to a system organ class and a preferred term. Treatment-emergent adverse events **(TEAE)** are events with an onset after the administration of the first dose of protocol-specified therapy. **Analyses of TEAEs will include DREs.**

Subject incidence of all **TEAEs**, serious **TEAEs**, **grade 3 or higher TEAEs, TEAEs** leading to interruption or withdrawal of protocol-specified therapy, and fatal adverse events will be tabulated by system organ class and preferred term in descending order of frequency.

Laboratory Test Results:

Shift tables between the worst post-baseline and baseline grades for selected laboratory parameters will be provided. Plots or other summaries over time will be presented for selected laboratory parameters including Ig, platelets, and liver parameters (ALT, AST, ɣ-glutamyl transferase, ALP, and TBL).

Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to blinatumomab and pembrolizumab for subjects in the Full Analysis Set. The number of cycles initiated, completed, discontinued, and re-started of blinatumomab and pembrolizumab will be summarized. In addition, the duration of therapy will be summarized by cycle and overall. The number and percent of subjects with dose modifications (eg, dose changes, dose interruptions) and reasons for modification will be summarized.

Vital Signs

The number and percentage of subjects with abnormal changes in systolic blood pressure, diastolic blood pressure and heart rate will be summarized.

Antibody Formation

The incidence and percentage of subjects who develop anti blinatumomab antibodies (binding and if positive, neutralizing) and anti-pembrolizumab antibodies at any time will be tabulated.

Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications from study day 1 through safety follow-up will be summarized by preferred term as coded by the World Health Organization Drug (WHODRUG) dictionary in the Safety Analysis Set. In addition, the number and proportion of subjects receiving anti-cancer therapies during long-term follow-up will be summarized by WHODRUG preferred term.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Trial Manager to the investigator. The written ICF is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered. A legally acceptable representative is an

individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign and date the ICF to attest that informed consent was freely given and understood. Refer to International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines, Section 4.8.9.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an Investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. After Amgen amends the protocol, investigator is to return the signed investigator's Signature page confirming agreement to continue participation in the study according to the amendment. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

In this study, enrollment will be done through a manual process managed by Amgen.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the Clinical Monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Quality, Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments, the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication

Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

13. REFERENCES

A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood*. 1997 Jun 1;89(11):3909-3918.

Advani A, Coiffier B, Czuczman MS, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. *J Clin Oncol.* 2010;28(12):2085-2093.

Andorsky DJ, Yamada RE, Said J, et al. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. *Clin Cancer Res*. 2011;17(13): 4232-4244.

A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognosis Factors Project. *N Eng J Med.* 1993;329(14):987-994.

Armand P, Nagler A, Weller EA, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. *J Clin Oncol*. 2013;31(33):4199-4206.

Barosi G, Carella A, Lazzarino M, et al. Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. *Haematologica.* 2005;90(9):1236-1257.

Blank C, Brown I, Peterson AC, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer Res*. 2004;64(3): 1140-1145.

Amgen Blinatumomab Investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Brookmeyer R and Crowly J. A confidence interval for the median survival time. *Biometrics.* 1982;29-41.

Chemnitz JM, Parry RV, Nichols KE, et al. SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. *J Immunol.* 2004;173:945-954.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586.

Clopper CJ and Pearson EG. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrica***.** 1934;26(4):404-413.

Coiffier B and Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? *Hematology Am Soc Hematol Educ Program*. 2016;1:366-378.

Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130:1800-1808.

Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A.* 2010;107(9):4275-4280.

Dang NH, Ogura M, Castaigne S, et al. Randomized, phase 3 trial of inotuzumab ozogamicin plus rituximab (R-InO) versus chemotherapy for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (B-NHL). ASCO Annual Meeting Proceedings. 2014;32(15).

Disis ML. Immune regulation of cancer. *J Clin Oncol*. 2010;28(29):4531-4538.

Dreier T, Lorenczewski G, Brandl C, et al. Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. *Int J Cancer*. 2002;100(6):690-697.

Dudley ME, Wunderlich JE, Yang, JC, et al. Adoptive Cell Transfer Therapy Following Non-myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma. *J Clin Oncol*. 2005;2346-2357.

Feuchtinger T, Feucht J, Kayser S, et al. Leukemia Related Co-Stimulation/Co-Inhibition Predict T-Cell Attack of Acute Lymphoblastic Leukemia Mediated by Blinatumomab. *Blood***.** 2015;126:3764.

Fiona K and Ruth P. Radioimmunotherapy (RIT) in non-Hodgkin lymphoma. *Targeted Oncology*, 2007;2(3):173-179.

Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene.* 2004; 23(38):6524-6534.

Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autommunity. *Immunol Rev*. 2010;236:219-242.

Friedberg W. Relapsed/refractory diffuse large B-cell lymphoma. ASH Education Program Book 2011; 2011: 498-505.

Gabellier L and Cartron G. Obinutuzumab for relapsed or refractory indolent non-Hodgkin's lymphomas. *Ther ad Hematol.* 2016;7(2):85-93.

Gisselbrecht C and Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. *Br I Haematol*. 2018;182(5):633-643.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*, 2010;28(27):4184-4190.

Goebeler M, et al. Blinatumomab (CD3/CD19 Bite (R) Antibody) results in a high response rate in patients with relapsed non-hodgkin lymphoma (NHL) including mantle cell lymphoma (MCL) and diffuse large B cell lymphoma (DLBCL). in ONKOLOGIE. 2011. KARGER ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND

Goy A, Younes A, McLaughlin P, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23(4):667-675.

Greenwald, RJ, Freeman GJ, Sharpe AH. The B7 Family Revisited. *Annu Rev Immunol.* 2005;23:515-548.

Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004. 103(1):275-282.

Hartge P and Wang SS. Overview of the etiology and epidemiology of lymphoma. *Non-Hodgkin's Lymphomas. Lippincott, Philadelphia*, 2004.711-727.

Hirano F, Kaneko K, Tamura H, et al., Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*. 2005;65(3):1089-1096.

Hunder NN, Wallen H, Cae J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med.* 2008;358(25):2698-2703.

Kalbfleisch JD and Prentice RL. The Statistical Analysis of Failure Time Data. *John Wiley, New York Rev*, 1980;4(2):25.

Kenderian SS, Ruella M, Shestova O, et al. Identification of PD1 and TIM3 As Checkpoints That Limit Chimeric Antigen Receptor T Cell Efficacy in Leukemia (Abstract). *Biol Bone Mar Transpl.* 2016; 22: S19-S481.[abstract]

Kiyasu J, Miyoshi H, Hirata A, et al. Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. *Blood.* 2015; 126(19):2193-2201.

Köhnke T, Krupka C, Tischer J, Knösel T, Subklewe M. Increase of PD-L1 expressing B-precursor ALL cells in a patient resistant to the CD19/CD3-bispecific T cell engager antibody blinatumomab. *J Hematol Oncol.* 2015;8(1):111.

Krupka C, Kufer P, Kischel R, et al., Blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: reversing a T-cell-induced immune escape mechanism. *Leukemia*. 2016;30(2):484-491.

Lazlo GS, Gudgeon CJ, Harrington KH, Walter RB. T-cell ligands modulate the cytolytic activity of the CD33/CD3 BiTE antibody construct, AMG 330 [abstract]. *Bl Cancer J*. 2015; 5: e340.

Lenz G, Staudt LM. Aggressive lymphomas. *N Engl J Med*. 2010;362(15):1417-1429.

Lenz G, Wright GW, Emre NC, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proc Natl Acad Sci USA*, 2008; 105(36):13520-13525.

Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase 1b Study. *J Clin Oncol.* 2016; 34(23):2698-2704.

Martelli M, Ferreri AJ, Agostinelli C, Di Rocco A, Pfreundschuh M, Pileri SA. Diffuse large B-cell lymphoma. *Crit Rev Oncol Hematol*. 2013;87(2):146-171.

Morgan G, Vornanen M, Puitinen J, et al. Changing trends in the incidence of non-Hodgkin's lymphoma in Europe. *Ann Oncol.* 1997;8(suppl 2):49-54.

Morschhauser F, Kraeber-Bodéré F, Wegener WA, et al. High rates of durable responses with anti-CD22 fractionated radioimmunotherapy: results of a multicenter, phase I/II study in non-Hodgkin's lymphoma. J Clin Oncol. 2010;28(23):3709-3716.

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med*. 2017;377:2531-2544.

Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res.* 2007;13(7):2151-2157.

Nyman H, Adde M, Karjalainen-Lindsberg ML, et al. Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Blood.* 2007;109(11):4930-4935.

Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci USA.* 2001;98(24):13866-13871.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.

Osada T, Patel SP, Hammond SA, et al. CEA/CD3-bispecific T cell-engaging (BiTE) antibody-mediated T lymphocyte cytotoxicity maximized by inhibition of both PD1 and PD-L1. *Cancer Immun Immunother*. 2015;64:677-688.

Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD01 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. *Mol Cell Biol.* 2005;25(21):9543-9553.

Pettengell R, Coiffier B, Narayanan G, et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol*. 2012;13(7):696-706.

Pilon-Thomas S, Mackay A, Vohra N, Mulé JJ. Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. *J Immunol*. 2010;184(7):3442-3449.

Riley JL. PD-1 signaling in primary T cells. *Immunol Rev.* 2009:0105-2896.

Roschewski M, Dunleavy K, Pittaluga S, et al. Circulating tumor DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. *Lancet Oncol,* 2015;16(5):541-540.

Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large B-cell lymphoma. *N Engl J Med.* 2002; 346(25):1937-1947.

Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood.* 2012;119(22):5126-5132.

Schlereth B, Kleindienst P, Fichtner I, et al. Potent inhibition of local and disseminated tumor growth in immunocompetent mouse models by a byspecific antibody construct specific for Murine CD3. *Cancer Immunol Immunother*. 2006;55(7):785-796.

Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007;109(5):1857-1861.

Sheppard KA, Fitz LJ, Lee JM, et al., PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett*. 2004;574(1-3):37-41.

Smith SM, van Besien K, Karrison T, et al. Temsirolimus has activity in non–mantle cell Non-Hodgkin's lymphoma subtypes: The University of Chicago Phase II consortium. *J Clin Oncol*. 2010;28(31):4740-4746.

Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. *J Immunother Cancer*. 2014;2:3.

Stopeck AT, Unger JM, Rimsza LM, et al. A phase II trial of single agent bevacizumab in patients with relapsed, aggressive non-Hodgkin lymphoma: Southwest oncology group study S0108. *Leuk Lymphoma*. 2009;50(5):728-735.

Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res*. 2003;63(19):6501-6505.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 Revision of the World Health Organization (WHO) Classification of lymphoid neoplasms. *Blood*, 2016;127(20):2375-2390.

Tilly H, Vitolo U, Walewski J, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Annals of Oncology*, 2015;26(supp5):116-125.

Trneny M, Verhoef G, Dyer MJS, et al. "Starlyte phase II study of coltuximab ravtansine (CoR, SAR3419) single agent: Clinical activity and safety in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL; NCT01472887)." ASCO Annual Meeting Proceedings. Vol. 32. No. 15_suppl. 2014.

Vacirca JL, Acs PI, Shimkus BJ, et al. Bendamustine/rituximab in relapsed or refractory diffuse large B-cell lymphoma. ASCO Annual Meeting Proceedings. Vol. 28. No. 15_suppl. 2010.

Viardot A, Goebeler M, Hess G, et al. Treatment of relapsed/refractory diffuse large B-cell lymphoma with the bispecific T-cell engager (BiTE®) antibody construct blinatumomab: primary analysis results from an open-label, phase 2 study. *Blood*. 2014;124(21):4460.

Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer --preclinical background: CTLA-4 and PD-1 blockade. *Semin Oncol*. 2010;37(5):430-439.

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. *Ann Oncol.* 2011;22(7):1622-1627.

Zelenetz AD, Gordon LI, Wierda WG, et al. Diffuse Large B-Cell Lymphoma Version 1.2016. *J Natl Compr Canc Netw*, 2016;14(2):196-231.

Zimmerman Z, Maniar T, Nagorsen D. Unleashing the clinical power of T cells: CD19/CD3 bi-specific T cell engager (BiTE(R)) antibody construct blinatumomab as a potential therapy. *Int Immunol*. 2015;27(1):31-37.

Zhang L, Gajewski TF, Kline J. PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model. *Blood*. 2009;114(8):1545-1552.

Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity*. 2004;20:337-347.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event grading and information. The CTCAE scale is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Reporting

To facilitate appropriate monitoring for signals of **Drug-induced liver injury (**DILI**)**, cases of concurrent **aspartate aminotransferase (**AST**)** or **alanine aminotransferase (**ALT**)** and **total bilirubin (**TBL**)** and/or INR elevation according to the criteria specified in Section 6.4 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate **case report form (**CRF**)** (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 6-5 or who experience AST or ALT elevations > 3 x **upper limit of normal (**ULN**)** or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, **alkaline phosphatase (**ALP**)**, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or **international normalized ratio (**INR**)** > 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin **G** (IgG), Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
- Prior and/or concurrent diseases or illness
- Exposure to environmental and/or industrial chemical agents
- Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
- Prior and/or concurrent use of alcohol, recreational drugs and special diets
- Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - **Creatine phosphokinase (**CPK**)**, haptoglobin, **lactate dehydrogenase (**LDH**)**, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Appendix B. Sample Serious Adverse Event Report Form (Sample eSerious Event Contingency Form – Paper Based Form)

AMGEN Study 20150290 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month ____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Blinatumomab: No ☐ Yes ☐ Pembrolizumab: No ☐ Yes ☐ <Device>: No ☐ Yes ☐ <Device>: No ☐ Yes ☐	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Prior to, or at time of Event Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Blinatumomab	☐blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Pembrolizumab	☐blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study 20150290 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study 20150290 Blinatumomab	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix C. Pregnancy and Lactation Notification Worksheets

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20150290

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (___)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** [ ] Female [ ] Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? [ ] Yes [ ] No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ [ ]Unknown [ ]N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? [ ]Yes [ ]No [ ]Unknown [ ]N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? [ ]Yes [ ]No [ ]Unknown [ ]N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20150290

Study Design: [X] Interventional [ ] Observational (If Observational: [ ] Prospective [ ] Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? [ ] Yes [ ] No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? [ ] Yes [ ] No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? [ ] Yes [ ] No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: [ ] Female [ ] Male

Is the infant healthy? [ ] Yes [ ] No [ ] Unknown [ ] N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix D. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5: 649-655

Appendix E. DLT Criteria (Part 1)

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0.

The occurrence of any of the following within the dose limiting toxicity (DLT) evaluation period

- 42 days from initiation of pembrolizumab treatment (DLT period begins on day 15 for Ia and day 19 for IIa and IIIa)

will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

Laboratory DLTs	
Hematologic Toxicity	• Any Grade 4 hematologic toxicity lasting ≥ 7 days except: – Asymptomatic anemia not resulting in transfusion • Grade 4 thrombocytopenia lasting < 7 days if associated with: – A bleeding event which does not result in hemodynamic instability but requires a platelet transfusion, or – A life-threatening bleeding event which results in urgent intervention and/or admission to an Intensive Care Unit
Non-hematologic Toxicity	• Grade ≥ 3 AST or ALT • Grade ≥ 3 bilirubin • Grade 3 or 4 laboratory value except: • Grade ≥ 3 chemistry that responds to medical intervention and resolves to grade ≤ 1 within 7 days • Grade 3 or 4 laboratory value that reoccurs
Non-laboratory DLTs	
Non-hematologic Toxicity	• Grade 5 toxicity • Any Grade 3 or 4 toxicity except: – Grade 3 CNS related events that resolve within 7 days with treatment interruption and routine medical management – Grade 3 CRS or tumor lysis syndrome that responds to intervention/treatment interruption and resolves to grade ≤ 1 within 7 days – Grade 3 fever, persistent for **≤** 7 days and clinically manageable by investigator discretion – Grade 3 infection, persistent for **≤** 7 days and considered controlled on anti-infective therapy by investigator discretion – Grade 3 febrile neutropenia, persistent for **≤** 7 days and considered controlled on anti-infective therapy by investigator discretion – Grade 3 vomiting, or diarrhea persistent for **≤** 3 days **with** optimal supportive care – Grade 3 nausea or abdominal pain persistent for **≤** 5 days **with** optimal supportive care

For a definition of DLT evaluable subjects, see Section 10.1.2.

Appendix F. Clinically Relevant Neurologic Events by High-level Group Term (HLGT)

Cranial nerve disorders (excluding neoplasms)
Demyelinating disorders
Encephalopathies
Mental impairment disorders
Movement disorders (including parkinsonism)
Neurological disorders NEC
Seizures (including subtypes)
Cognitive and attention disorders and disturbances
Communication disorders and disturbances
Deliria (including confusion)
Dementia and amnestic conditions
Disturbances in thinking and perception
Psychiatric disorders NEC
Schizophrenia and other psychotic disorders

Appendix G. Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.2.2.2.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Pneumonitis:

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea suspecting colitis should consider gastrointestinal (GI) consultation and performing endoscopy to confirm or rule out colitis.

- For Grade 2 or 3 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (T1DM) (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

For T1DM or Grade 3-4 Hyperglycemia:

- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (eg propranolol or thionamides) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care
- Grade 3-4 hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered

Hepatic:

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

- For Grade 2 events, treat with corticosteroids.
- For Grade 3-4 events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 14-1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 14-1. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg from 100 mL/hr. to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Footnotes defined on last page of table.

Table 14-1. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

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Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov
CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug

Appendix H. Additional Potential Exploratory Biomarker Research

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the subject population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

Biomarker research to identify factors important for which blinatumomab and pembrolizumab therapy may be pursued. For example, pre and postdose bone marrow biopsies/aspirates, lymph node biopsies and blood samples from this study may undergo flow cytometric, proteomic, genomic, and transcriptional analyses at a central laboratory. Lymph node biopsies and blood samples will be evaluated using DNA sequencing. Utilizing both pre and post-treatment tumor biopsies and/or blood samples (serum or plasma), change in baseline of candidate biomarkers will also be assessed.

Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets. In addition, biomarker assay characterization may be performed to evaluate factors important for the identification of biomarkers.

Assays may include but are not be limited to:

<u>Multiplex Flow Cytometric Analysis</u>

Emerging data suggest that blockade of the PD-1/PD-L1 pathway results in enhanced T-cell mediated immune response. To test the hypothesis that T-cell activation mediated by blinatumomab and pembrolizumab treatment correlates with clinical response, total T-cell count and T-cell subsets in peripheral blood, eg, Naïve, activated, memory and regulatory T cells, will be assessed pre and postdose and in both responders and nonresponders. Natural killer (NK) cells enumeration will also be performed pre and postdose in both responders and nonresponders.

<u>Transcriptional Analyses</u>

Messenger RNA (mRNA) expression profiling in archival material, lymph node samples, and blood samples will be completed to assess gene expression and to attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that blinatumomab and pembrolizumab responders will exhibit a “stalled cytotoxic

T lymphocyte (CTL)" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (eg, weak but discernible) interferon-gamma transcriptional program will be detectable by profiling analyses. Global profiling may also be pursued.

Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (eg, IL-10).

Gene Sequencing

New data are emerging that suggest we can define certain tumor types as having high mutational burden. There is a potential that this hypermutated state may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state may correlate with nonresponse.

Genome-wide whole exome sequencing (WES) may be performed from archival material, lymph node samples, and blood samples to assess genomic events such as but not limited to mutational burden as well as to evaluate fusion and amplification events such as 9p24.1 amplification.

Future Biomedical Research

The sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Planned Genetic Analysis

Planned **genetic** analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting **planned genetic analysis**, or if the IRB/IEC does not approve the **planned genetic analysis of collected samples**, then this **analysis will not be completed**. **For lab samples** collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the future biomedical research (FBR) consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the procedure manual.

Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of FBR:

- Leftover DNA for future use
- Leftover bone marrow biopsy/aspirate samples
- Leftover tissue samples
- Leftover lymph node biopsies

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to Amgen or non-Amgen investigational products to investigate and further understand DLBCL.

Tumor biopsies are to be collected and pharmacodynamic changes analyzed to determine the effect of the drug on target(s) in the tumor as well as to potentially analyze molecular mechanisms associated with acquired resistance.

Appendix I. Response Assessment per the Lugano Classification 2014

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

The Deauville five point scale. The scale scores the most intense uptake in a site of initial disease, if present.

Score	Definition
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Moderately increased uptake compared to the liver
5	Markedly increased uptake compared to the liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Appendix J. Revised Response Criteria for Malignant Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Cheson et al, 2007

Amendment 5

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B Cell Lymphoma (DLBCL)

Amgen Protocol Number (Blinatumomab) 20150290

Amendment Date: 03 December 2019

Rationale:

The main purpose of this protocol amendment is to:

- Remove patient reported outcome (PRO) assessments and the central vendor read from the phase 1b study to streamline the data collection and assessments in this phase 1b study that has the primary endpoint of MTD and safety.
- Update and clarify eligibility criteria to provide clearer definitions and more feasible guidance based on the feedback from study sites and experience from the study conduct.
- Other administrative updates for consistency and optimization of SoA (schedule of assessments), such as: timepoints of PK and PD sample collection, adjustment of schedule after blinatumomab dose interruption.

Amendment 4

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Amgen Protocol Number (AMG 103/Blinatumomab) 20150290

Merck Protocol Number: PN348

EudraCT Number: 2016-002191-27

NCT Number: NCT03340766

Amendment Date: 18 July 2019

Rationale:

This protocol is being amended to:

- Update Figure 1 and its footnotes to maintain relevancy.
- Update language for escalating to an intermediate dose less than maximum tolerated dose (MTD) for cohort expansion or adjudication of dose limiting toxicity (DLT) criteria
- Removal of text for interactive voice response system (IVRS)
- Clarify that the Dose Level Review Team (DLRT) will meet to review safety data for criteria including if in 2 or more subjects out of 6**,** a DLT has been reported, or in 3 or more subjects out of 10, a DLT has been reported in a cohort
- Update assessment language that subjects who receive at least 1 full dose of pembrolizumab who discontinue from all study treatment in cycle 1 shall undergo a positron emission tomography (PET)/computed tomography (CT) scan between 14 to 28 days after last pembrolizumab exposure
- Update the language for the serious disease related events and serious adverse events.
- Update immune panel and serum cytokine assessments for cohorts IIa and IIIa
- Update the subgroup region of USA/Canada to North America

- Clarify that the DLRT members do not need to consist of at least 1 statistician
- Reverse removal of neutropenia lasting ≥ 7 days (not associated with fever or infection) from hematologic toxicity from laboratory DLTs
- Replace the outdated pregnancy and lactation notification forms with updated forms.
- Make editorial and administrative updates

Superseding Amendment 3

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Amgen Protocol Number Blinatumomab 20150290

Merck Protocol Number PN348

Eudra CT number 2016-002191-27

Amendment 3 Date:	08 February 2019
Superseding Amendment 3 Date:	25 March 2019
Superseding Amendment 3 Date:	11 April 2019

Rationale:

This protocol is being amended to:

- Correct study design language to more accurately reflect rolling 6 study design:
  - Update dose limiting toxicity (DLT) and maximum tolerated dose (MTD) definitions and clarify DLT evaluable analysis set
  - Clarify Dose Level Review Team (DLRT) options, including utilization of expansion cohorts
- Remove simultaneous dosing cohorts (Ib, IIb, IIIb) so subjects reach presumed therapeutic dose of blinatumomab more quickly; as a result the total number of subjects enrolled in Part 1 was adjusted
- Replace de-escalation program with a more straightforward binatumomab 9 to > 28 µg/day, 9 to > 28 to > 56 µg/day and 9 to > 28 to > 112 µg/day design
- Clarify Inclusion Criteria 103 for histologically confirmed Diffuse Large B Cell Lymphoma in light of prior therapies
- Clarify Inclusion Criteria 112 to allow for incisional biopsy as well as excisional biopsy, as excisional biopsy often not feasible/safe in patients with bulky disease
- Remove Exclusion Criteria 210 to allow transfusion of blood products or colony stimulating factors if indicated within 14 days prior to first day of study treatment
- Require an early safety follow up visit if subject starts new anti-lymphoma treatment
- Require positron emission tomography (PET)/computed tomography (CT) 14 to 28 days after last pembrolizumab exposure for subjects who discontinue during Cycle 1

- Modify pre-dose dexamethasone timeframe to 6 hours prior to start of treatment in each treatment cycle, and within 6 hour prior to each dose step due to dexamethasone half-life.
- Remove International Prognostic Index (IPI) from Screening
- Remove PAXgene as no longer required
- Remove Self Evident Correction wording due to Sponsor process update
- Added usage of Interactive Voice Response System (IVRS) for Part 2 expansion portion of study
- Clarified programmed death ligand-1 (PD-L1) exploratory endpoint language Section 10.1.1.4
- Clarified pseudo-progression language in Section 7.13.12.4
- Updated key sponsor contacts and minor editorial changes

Additional administrative errors were identified and rectified in the superseding protocol amendment 3 (dated 25 March 2019):

- Correct Exclusion Criteria numbering
  - 210 was deleted in protocol amendment 3, so numbering sequence was corrected from 209 to 211
  - 223 was deleted in protocol amendment 2, so numbering sequence was corrected from 222 to 224
- Re-introduced “a” to the cohort groups in Appendix E to align with study design
- In reference to current Cheson criteria nomenclature, complete or partial response was changed to complete or partial remission in relevant areas of the protocol
  - A reference was added under secondary endpoints to note that remission in this context equates to response under the new Cheson Criteria (2007) classification

A second superseding amendment (dated 11 April 2019) was completed to correct the dates on the title page of the superseding protocol amendment 3:

- Correct the date of Protocol Amendment 3
- Add the date of Superseding Protocol Amendment 3

Amendment 3

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Amgen Protocol Number Blinatumomab 20150290

Merck Protocol Number PN348

Eudra CT number 2016-002191-27

Amendment 3 Date:	08 February 2019
Superseding Amendment 3 Date:	25 March 2019

Rationale:

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  - Update dose limiting toxicity (DLT) and maximum tolerated dose (MTD) definitions and clarify DLT evaluable analysis set
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Amendment 3

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Amgen Protocol Number Blinatumomab 20150290

Merck Protocol Number PN348

Eudra CT number 2016-002191-27

Amendment Date: 08 February 2019

Rationale:

This protocol is being amended to:

- Correct study design language to more accurately reflect rolling 6 study design:
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- Remove PAXgene as no longer required
- Remove Self Evident Correction wording due to Sponsor process update
- Added usage of Interactive Voice Response System (IVRS) for Part 2 expansion portion of study
- Clarified programmed death ligand-1 (PD-L1) exploratory endpoint language Section 10.1.1.4
- Clarified pseudo-progression language in Section 7.13.12.4
- Updated key sponsor contacts and minor editorial changes

Amendment 2

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Amgen Protocol Number Blinatumomab 20150290

Merck Protocol Number PN348

Eudra CT number 2016-002191-27

Amendment Date: 08 March 2018

Rationale:

This protocol is being amended to:

- Update Merck investigational product background information (pembrolizumab) and rationale for dose selection
- Include language about addition of pembrolizumab to blinatumomab dosing per once blinatumomab target dose has been reached.
- Update End of Study language per new protocol template.
- Update Exclusion Criteria #222 to indicate that subjects who have quantifiable hepatitis b virus are excluded.
- Add Exclusion Criteria #227 for history of solid organ transplant.
- Update dose modification for pembrolizumab (text and table).
- Update concomitant medication language per Merck text.
- Add hepatitis antibody testing at screening and hepatitis virus testing throughout study.
- Add neurological exam to physical exam.
- Clarify PK language for expansion cohort.
- Add suspected unexpected serious adverse reaction (SUSAR) language to safety section.
- Clarify ± 3 day window for pembrolizumab-related assessments
- Make administrative and editorial changes.

Amendment 1

Protocol Title: A Phase 1b Open Label Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adult Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

AMG 103/Blinatumomab

MK-3475/Pembrolizumab

Amgen Protocol Number (AMG 103/Blinatumomab) 20150290

Merck Protocol Number PN348

EudraCT number 2016-002191-27

Amendment Date: 21 August 2017

Rationale:

This protocol is being amended in response to queries received by the Food and Drug Administration (FDA) and administrative updates. Changes to the protocol include:

- Removal of phase 3 from the study (including removal of Standard of Care chemotherapy)
- Update study schema and design to add new cohorts, change dosing schedules
- Update number of subjects and statistical analysis sections based on phase 1 study design
- Remove references to phase 1b, since this is now a single phase study
- Update cohorts so that cohorts IIa and IIIa start on pembrolizumab on 19 and cohort Ia starts on pembrolizumab on day 15.
- Update DLT periods
- Modify eligibility criteria to include previous therapies, removal of Glucksberg criteria, and to update other malignancy language for alignment with other blinatumomab studies
- Update Dose Level Review DLRT language
- Clarification of PET scan and CT scan windows
- Update pembrolizumab language to align with other pembrolizumab studies
- Update blinatumomab mechanism of action based on updated IPIM wording (added further detail about dual binding specifity)
- Added ± 3 day window for scans on study
- Update dose modification for pneumonitis to include recurrent Grade 2.
- Administrative and editorial edits for clarity and consistency throughout protocol

Approval Signatures

Document Name: Protocol-Published Amendment Blinatumomab 20150290 5

Document Description:

Document Number: CLIN-000276029

Approval Date: 10 Sep 2021

Type of Study Protocol: Amendment

Protocol Amendment No.: 5

Document Approvals	
Reason for Signing: Functional Area	Name: Gerhard Zugmaier Date of Signature: 10-Sep-2021 13:56:55 GMT+0000